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TABLE OF CONTENTS

William Harvey, Neurologist Sir RUSSELL BRAIN, BT., D.C.L., LL.D., D.M., F.R.C.P. 899

Field Trial of Influenza Virus Vaccine in Patients with Chronic Bronchitis During the Winter 1957–8
REPORT BY JOINT WORKING PARTY OF THE MEDICAL RESEARCH COUNCIL AND OF THE BRITISH TUBERCULOSIS ASSOCIATION 905

Inoculation of Human Volunteers with Parainfluenza Viruses Types 1 and 3 (HA 2 and HA 1)
D. A. J. TYRRELL, M.D., M.R.C.P., M. L. BYNOE, M.B., D.T.M.&H., K. BIRKUM PETERSEN, R. N. P. SUTTON, B.M., D.C.H., and MARGUERITE S. PEREIRA, M.B. 909

Antibodies to Haemophilus Influenzae in Chronic Bronchitis A. A. GLYNN, M.B., M.R.C.P. 911

Accidental Injection of Thiopentone into Arteries J. B. KINMONTH, M.S., F.R.C.S., and R. C. SHEPHERD, F.R.C.S. 914

Gangrene of Forearm After Intramuscular Chlorpromazine R. J. HAMER HODGES, F.F.A. R.C.S., D.A. 918

Werner's Syndrome (Progeria of the Adult)
M. W. J. BOYD, M.D., M.R.C.P.Ed., and ALAN P. GRANT, M.D., F.R.C.P.I., M.R.C.P. 920

Epidemiology of " Sudden, Unexpected, or Rapid " Deaths in Children JOHN L. EMERY, M.D., D.C.H. 925

Diuretic Effect of Hydroflumethiazide J. H. JONES, M.B., M.R.C.P., and J. VERRIER JONES, B.M., M.R.C.P. 928

Hypothermia After Chlorpromazine in Myxoedematous Psychosis J. R. A. MITCHELL, M.B., M.R.C.P., D. H. C. SURRIDGE, B.M., B.Ch., and R. G. WILLISON, B.M., M.R.C.P.Ed. 932

MEDICAL MEMORANDA

Problem of Cooling a Gangrenous Leg. J. KOHARI, F.R.C.S.Ed. 933

BOOK REVIEWS 935

DRUG TREATMENT OF DISEASE

Corticosteroids in Treatment of Skin Diseases—I. F. RAY BETTLEY, T.D., M.D., F.R.C.P. 943

GENERAL ARTICLES AND NEWS

B.M.A. Annual Clinical Meeting 945
BIRTH OF A HOSPITAL 950
NEW APPLIANCES 950
MEDICAL NOTES IN PARLIAMENT 962
VITAL STATISTICS 963
MEDICAL NEWS 965
QUESTIONS AND COMMENTS 967

OBITUARY

J. C. Meakins, C.B.E., M.D., C.M., LL.D., F.R.C.P., F.R.C.P.Ed., F.R.C.P.C., HON. F.R.C.S.Ed., F.A.C.P. 959
S. J. Cameron, LL.D., M.B., Ch.B., F.R.F.P.S., F.R.C.O.G. 960
Sir James Elliott, M.D., LL.D., F.R.A.C.S., F.A.C.S. 960
John Livingston, M.D., F.R.C.S.Ed. 961
T. O. Jones, L.R.C.P.&S.Ed. 961
L. S. Bruce, M.B., Ch.B. 962

LEADING ARTICLES

Behaviour of the Market Place 937
Diuretics Unlimited 938
Bed Rest in Acute Nephritis 939

ANNOTATIONS

A New Penicillin 940
Radioactive Contamination of Food 941
Visual Defects in Children 941
Treatment of Venereal Diseases Outside Hospitals 942

CORRESPONDENCE

Consciousness during Surgical Operations. C. LANGTON HEWER, F.F.A. R.C.S.; CECIL GRAY, F.F.A. R.C.S., and IAN C. GEDDES, F.F.A. R.C.S.; JOHN GORDON, F.F.A. R.C.S. 951
Primigravidae in Rented Rooms. JOHN C. DARNLEY, M.R.C.S. 951

SUPPLEMENT

Full Contents on First Page of Supplement
Proceedings of Council 147
General Medical Services Committee 151
Public Health Committee 153
Correspondence:
Theatre Orderlies. A. M. A. MOORE, F.R.C.S.; F. C. RADFORD, L.I.B.S.T. 157
Deputizing Arrangements. G. ROSEMONT, M.B. 157

CORRESPONDENCE—*contd.*

Earliest Symptoms of Measles. HAMISH MACLEAN, M.B. 952
Tongue-tie. DENIS BROWNE, F.R.C.S. 952
Service Psychiatrists. H. E. S. MARSHALL, M.C., D.P.M.; J. F. WILDE, M.D., D.P.M.; W. S. PARKER, M.B.; T. W. PRESTON, M.D.; FREDERICK DILLON, M.D.; J. TODD, D.P.M.; J. NEWCOMBE, M.B., D.P.M. 952
Fees for Drug Trials. E. CRONIN, M.D. 954
Press Publicity. DONALD V. BATEMAN, F.F.A. R.C.S. 954
The Norwich Meeting. A. TALBOT ROGERS, M.B., B.S.; RALPH A. NOBLE, M.B. 955
German Medicine Abroad. A. P. CAWADIAS, F.R.C.P. 955
Dietary Fat and Serum Cholesterol. C. GOPALAN, M.D., and S. G. SRIKANTIA, M.B. 956
Reversible Mutations. D. STARK MURRAY, M.B. 956
Dilatation and Curettage. ALBERT DAVIS, F.R.C.S. 957
Birth Weight and Maternal Smoking. C. R. LOWE, M.D. 957
Treatment of Migraine. MARY G. H. EDWARDS, M.R.C.S. 957
New Sulphonamides. J. R. HARPER-SMITH, L.R.C.P.I. 957
Letters on other subjects appear on p. 958

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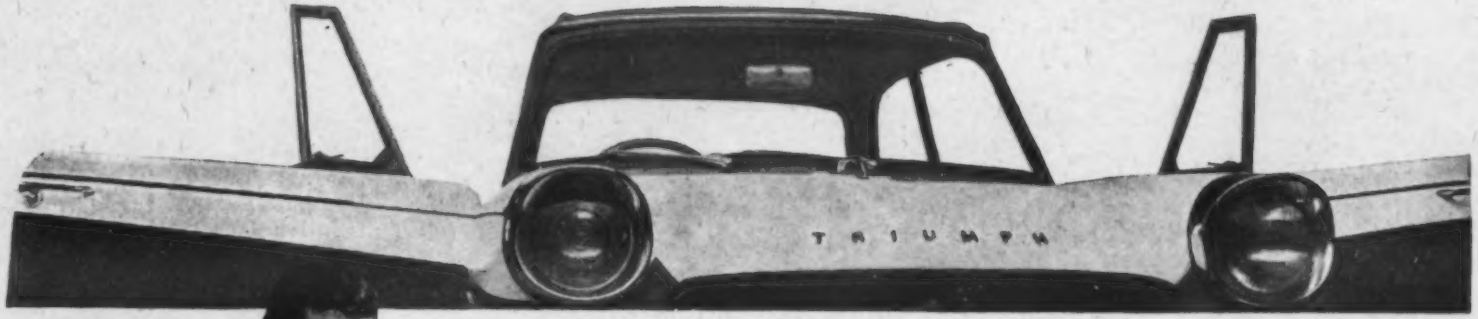

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 7 1959

WILLIAM HARVEY, NEUROLOGIST*

BY

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The first injunction laid by William Harvey upon the Harveian Orator is that the Oration shall be "a commemoration of all the Benefactors of the said College by name." This practice has fallen into disuse, perhaps because the benefactors became too numerous, but I propose to make an exception in this historic year. I am sure it would be Harvey's wish that I should express our gratitude to the Wolfson Trustees for their magnificent gift to the College, which will do so much to enable it to meet the growing demands upon it, and to maintain in a future which will far outlast our individual lives those immortal traditions to which Harvey himself so greatly contributed.

Next, Sir, may I thank you for the honour you have done me in choosing me for this distinguished office, which I appreciate not only for the honour it is, but also because, during the last year, I have often felt as though at your bidding I were living in the seventeenth century, in which I have come to know William Harvey afresh and admire him the more as one belonging to that rare genus of geniuses the comprehensive man.

And I cannot better carry out Harvey's second injunction—to exhort our Fellows and members "to search and study out the secrets of Nature by way of experiment"—than by offering them Harvey himself as an example. And surely it is through a common devotion to the science and art of medicine that they may best "continue in mutual love and affection amongst themselves."

It is sometimes thought that three hundred years after Harvey's death there can be nothing new to say about him. I am sure that is not true. But as this year's Orator I am peculiarly fortunate in being able to comment upon a new book by Harvey, published for the first time within the last year, the *De motu locali animalium*,[1] translated by Dr. Gweneth Whitteridge, on whose work I have freely and gratefully drawn. This book, however, is available for all to read, and, so far as it embodies the views on muscular action traditional in Harvey's day, it may be thought to be interesting but perhaps unexciting. If, however, it is considered in relation to two of his other works, the *De generatione*[2] and the *Prelectiones*,[3] it becomes possible to extract from the three together a fairly coherent idea of his conception of the functions of the nervous system. And from these and other sources we can glean evidence of his clinical observations in the sphere of nervous disease. I hope to show that Harvey, though he was not an original contributor to our knowledge of neurology, nevertheless had what was, for the times in which he lived, a quite exceptional interest in the functions of the nervous system, and grasp of the problems which neurology presents, and that in some interesting respects his insight anticipates the conclusions which later workers, with facilities which he lacked, were able to reach.

Harvey, like all his contemporaries, was so dependent upon the work of his predecessors that it is sometimes difficult to decide which of his ideas were original and which were derived from accepted authorities. Indeed, it would be impossible to be sure about this without having read at least all Aristotle, Galen, Vesalius, and Fabricius wrote, which I cannot claim to have done. Nevertheless, this is perhaps not very important, partly because I am more concerned to present the ideas in Harvey's mind than to decide how far they were original, and partly because Harvey does sometimes himself identify his own ideas by the use of his particular symbols or otherwise.

Functions of the Nervous System as Conceived in Harvey's Day

If we are to appreciate Harvey's critical judgment we must first be familiar with the general views of nervous function current in his time. We may begin with Galen, whose own observations had added considerably to the knowledge of neurophysiology and who was still a dominant influence. Galen had observed that dividing the spinal cord paralysed the body below the level of the lesion, that its hemisection had this effect only upon that side on which the lesion was made, and that longitudinal section did not produce paralysis. He noted that injury of the recurrent laryngeal nerves made an animal dumb, and that this happened, too, when the intercostal muscles were cut, which also abolished expiration, the same effect being produced by dividing the intercostal nerves.[4] To explain these observations it was necessary to suppose that some exciting stimulus passed from the brain down the spinal cord through the intercostal nerves to the muscles, to cause their contraction. What was the nature of the stimulus?

Vesalius[5] expressed Galen's views when he wrote: "The brain . . . produces . . . the finest and subtlest of all (the three spirits, namely) the animal spirit. This it uses partly for the divine operations of the Reigning Soul, partly, however, it distributes it continuously to the organs of sense and motion through the nerves, as through little tubes." This animal spirit, Galen thought, came from the cerebral ventricles, where it had been formed by the brain from the vital spirit reaching it from the heart. From the ventricles it flowed to the cranial nerves, spinal cord, and peripheral nerves.

The idea that the nerves were hollow tubes was a very old one, having apparently originated with Alcmaeon of Croton, who lived in the fifth century B.C. and discovered the optic nerves, and probably derived the

*The Harveian Oration, delivered at the Royal College of Physicians of London on October 19, 1959.

idea of their hollowness from observing their subarachnoid spaces. Galen clearly had some doubts about this, for he said: "We cannot absolutely pronounce whether the power flows from the brain through the nerves to the limbs and the essence of the spirit reaches the feeling and moving parts; or whether it in some way or other strikes the nerves so as to induce in them a powerful change which is propagated through the parts to be moved, whether there is in each nerve an innate spirit belonging to it, which is struck by something coming as a sort of messenger from the first principle; or whether the spirit flows from the brain to parts on every occasion when we will to move them; or whether in the third place there is merely a change in the qualities of parts contiguous to each other (which appears to me to be hinted at by some who say that the influence is a power without a substance) I am not able easily to determine."[6]

Galen distinguished between motor and sensory nerves, though he thought that both were efferent, carrying impulses from the brain. "Through some nerves," he wrote, "the brain transmits the power of sensation to the parts below, through others voluntary movement. It is intelligible that all the nerves should have both these powers, but the soft are more suited for sensation, the hard for movement."[4] Vesalius, like Galen, kept an open mind about the nature of the nerve-impulse, but introduced a variation into the Galenic alternative—namely, that it might be conducted "through passages in the nerves, as is the vital spirit through the arteries, or along the surface of the nerves, like the ray of light along a column, or simply through the continuity of the nerves." Fabricius, whose views as Harvey's teacher are important, attributed muscular contraction to an impulse from the brain and spinal cord passing to the muscle through the hollow nerves.

In Harvey's time the cerebral ventricles were held to be the site of certain mental faculties. The origin of this doctrine is discussed by Pagel.[7] It was unknown to Galen, and appears to have been originated by the Christian writer Nemesius, Bishop of Emesia. Nemesius allocates the middle cerebral ventricle to cogitation and reason, the anterior to sensation, and the posterior to memory. St. Augustine also accepted the ventricular location of mental functions, of which he put forward two alternative schemes. Vesalius, however, rejected these ideas on the ground that the ventricles could hardly be associated with the higher human faculties when they were all present in so many stupid animals, notably the ass. These, then, are the broad outlines of the theories of nervous function which were generally held in Harvey's day.

Muscular Contraction

Harvey's new book, the *De motu locali animalium*, as Dr. Whitteridge points out in her introduction, consists of notes for a treatise, begun in 1627, added to on several occasions, but never cast into a final literary form. There had been a number of works with similar titles by previous authors to whom Harvey is obviously much indebted, notably Aristotle, Galen, and Fabricius*. Indeed, the first seven chapters of Harvey's book are, as Dr. Whitteridge has shown, "an examination, or rather a rehearsal with a certain amount of comment, of Aristotle's teaching concerning movement, and animal movement in particular." Much of this deals with the mechanics of muscular action, and is of no particular interest. As Dr. Whitteridge says, "the statement (Chapter 2) that 'nothing can both move itself and be moved in relation to the same action' makes clear the difficulty of thinking about action and reaction in the days of pre-Newtonian mechanics. Harvey mentions in this connection the action of leaping out of the stern of a boat (p. 56), but as he says no more about it one is left to wonder whether he was interested in the reaction of the boat." However, as the previous line contains the illustration of "two men striving against each other back to back" it is possible that Harvey was dimly anticipating Newton's third law.

Harvey's predecessors were divided on the nature and origin of the contractile elements in muscle. I have not time to discuss this controversy in detail now.[8] Fabricius accepted the Vesalian view that muscle developed out of the tendons, which were the main contractile element. Harvey, in Chapters 10 and 11 of the *De motu locali animalium*, discusses all the arguments of Fabricius and makes it clear that he himself considers the flesh to be the main factor in muscular contraction.

Tonic Movement

After discussing the mechanics of movement, he introduces a distinction between movements such as pushing or pulling, which we may term active movements, and what he calls "tonic movement." "Tonic movement" is a term used even before Galen chiefly to denote sustained muscular contraction. Harvey's discussion of it is an excellent illustration of how his mind worked, getting ideas from observations on insects and birds, brooding on their implications, and groping towards new conceptions. "Tonic movement," he says, "occurs in the case of the water-snake, the spider, and, very evidently, birds" (*D.m.l.* 27).† A little later he explains the significance of the spider. "While I was pondering these things I saw a spider as if divinely sent borne through the air by an invisible thread spun from its own body, yet it held on to the filament with its feet in tonic movement as Mr. Parson's buzzard on a fowl" (*D.m.l.* 29). "Tonic motion," therefore, means "to be contracted, to remain contracted, to keep the muscle tense and still in tonic motion: △ a kite‡ in the wind, a trout in a stream" (*D.m.l.* 65).

Later Harvey says, "Examples of [tonic motion or lineal contraction] are seen in the trout and the kite, in tetany, in keeping something contracted" (*D.m.l.* 119), and these illustrations are shortly afterwards (p. 121) amplified in the statement: "Tonic movement is required to stay still in a stream or on sand and by its means does a kite hover in the wind and a trout hang in a torrent." It is characteristic of Harvey that while Galen[9] illustrates "tonic motion" by "any bird" and "someone who swims against a current," and Fernel[10] speaks merely of "a bird," Harvey thinks specifically of a kite and a trout. He continues: "There are two kinds of tonic motion, either of the whole animal as in the case of the kite, or of the parts. Tonic motion of the parts occurs, according to Galen, when two muscles act in opposition to each other whose

*Aristotle's *De partibus animalium*, *De motu animalium*, and *De incessu animalium*; Galen's *De usu partium corporis humani*, and *De motu musculorum*; and Fabricius's *De motu locali animalium*.

†To make it possible to refer to the quotations from Harvey's writings, I have adopted the following abbreviations. *D.m.l.* for *De motu locali animalium*. *D.g.* for *De generatione*. *P.* for *Prelectiones*; in each case followed by the page number. In the only published edition of the *Prelectiones* both sides of each sheet have the same page number. I have therefore indicated the left-hand page by the page number alone and the right-hand page by the page number with c. (for contra). The full particulars of these books are given in the list of references.

‡The bird, not the toy.

weakness gives tremor, △ balance needle; when one muscle is contracted in sleep, sphincter etc., whose weakness gives relaxation; when several synergists work to produce stillness by acting either altogether, by turns or in part: △ in putting down, in sitting, and again in regulating the antagonists: flitter, fly, plane . . . " (*D.m.l.* 121). Here we find the germ of the idea that tonus, as sustained muscular contraction, is responsible for the posture either of a part of the body or of the body as a whole.

How does a trout maintain its position in a swiftly moving stream? An expert tells me that it is done "by means of continuous slight swimming movements. These involve principally almost imperceptible movements of the tail, with perhaps occasional steering movements of the other fins. When they are maintaining station in clear water it is known that they do it visually."[11] Retinal impulses, then, evoked by movement of the fish relative to the stream bottom stimulate the appropriate slight swimming movements necessary for the fish to maintain station. The kite and the kestrel, of course, maintain their position in much the same way, hovering with rapid but very small wing-beats, and since the bird's eyes are on the ground visual stimuli may well act as in the trout. It is characteristic of Harvey that he distinguishes the three types of flight which he describes as "flitter, fly, plane." Flitter denotes the rapid wing-movements of the hovering kite or kestrel; fly the wing-beats of a bird moving from one place to another; and plane the movement of the bird as a whole while its wings are fixed in "tonic motion" as it uses an upcurrent to move forwards along a cliff-face or, like the glider, to soar circling upwards lifted by a thermal. "The eagle and the kite," said Harvey, "plane, striving against the movement and fluctuation of the air" (*D.m.l.* 57).

It is also typical of Harvey that he saw the homology between the tonic movement of the spider, "divinely sent," paying out its invisible thread with all its legs in flexion, and Mr. Parson's buzzard on the fowl. Harvey must have seen many buzzards: what made him mention this one? We can only guess, but I suspect that Mr. Parson must have reported to Harvey as something exceptional its tonic grasp on the fowl, perhaps after it was captured, or even killed.

This makes it clear why for Harvey sustained muscular contraction and alternating movements merged into one another, and he found evidence of this in disease. "Tonic movement when it waxes and wanes creates tremor, namely, whenever, on account of weight, strength is required there tremor indicates weakness: △ . . . in the heels" (*D.m.l.* 57). It seems likely that this last reference is a description of ankle clonus. "In old men tremor begins in the head and in the hands when they are kept extended for a long time holding up weights. . . . When strength goes the shakings are frequent and more afflicting" (*D.m.l.* 57) Here tremor is correlated both with disturbances of muscle tone and with weakness.

Harvey made some acute observations on the role of the antagonists in muscular action. Commenting on Galen's view that in relaxation the muscles in part act and in part are moved, Harvey says, "but they are antagonists, for their task is partly to maintain a retarded and regulated action, △ laying down a wegge, going dancing etc. . . . in relaxation, the muscles in part both are moved and move and in part are moved but do not act" (*D.m.l.* 57). "If the action is to be made in the regulated manner," he writes, "then the necessary relaxation is also regulated, △ the tibialis muscles when sitting down and tapping with the foot" (*D.m.l.* 119). And again, "to set aside or put down by quietly opposing resistance [to its weight] is seen to be a combination of tonic movement and relaxation and to be half-way between doing and making. It occurs in sitting down, in leaping in dances, in dancing in any part, in laying down something with the hand" (this explains the earlier reference to "laying down a wegge"), "in nodding; in regulated movement, as that of a somewhat paralysed neck, the antagonists are moved correspondingly fast or slow in equilibrium. Wherefore there are degrees of movement: perceptible movement, relaxation, and tonic movement" (*D.m.l.* 141 and 143). This was perhaps as near as unaided observation could get to the idea of the inhibition of antagonists.

The Organization of Movement

In the fifth chapter of the *De motu locali animalium* Harvey discusses the classification of different types of movement made by his predecessors, especially Aristotle, Galen, and Fabricius, with special reference to the extent to which they are under voluntary control. Different types of movement had in the past been attributed to supposedly different parts of the soul, the vegetative part, the nutritive part, etc. Harvey was clearly dissatisfied with this theorizing, and at the end of the chapter puts forward his own view. In the existing state of knowledge this was necessarily very incomplete, but its chief interest lies in the fact that it is a unified view, which makes no demand upon any hypothetical functions of the soul. Harvey writes: "Should we not rather say this? Movements of the organs are all connected with the animal parts and cannot be divorced from the animal. Of these, some which arise from the needs of the body or from the will are to some greater or lesser degree under our control, as respiration, defecation and the movements of muscles in general, while other movements are entirely not under our control. Or again, some movements continue indefinitely, as the movement of the pulse and respiration, defecation and vomiting; others do not continue indefinitely and these are performed in accordance with Nature's demands, that is, they are dictated by the will or the needs of the body, while others are beyond natural needs and are dictated by the emotions" (*D.m.l.* 45).

The existence of involuntary movements led him to two important conclusions. The first was that organs which are the site of such movements must be supplied with some form of sensation which does not enter consciousness. "As there are some actions and motions the government or direction of which is not dependent on the brain, and which are therefore called *natural*, so also is to be concluded that there is a certain sense or form of touch which is not referred to the common sensorium, nor in any way communicated to the brain, so that we do not perceive by this sense that we feel" (*D.g.* 432).

Harvey's second conclusion is that whereas voluntary movements are under the control of the brain, involuntary movements are not. The evidence for this is derived partly from experience, partly from experiment. Discussing vomiting and diarrhoea as the results of movements of the stomach and bowels, he says: "As it lies not in our power either to provoke or to restrain

their motions, neither are we aware of any sensation dependent on the brain which should arouse the parts in question to motions of the kind" (*D.g.* 431). The other evidence is experimental, and here is one of the two experiments described by Harvey in the *De motu locali animalium*. "△ a cock's head off, the arteries being ligatured and artificial ventilation being given, movements are seen to persist but they are as the movements of men in delirium and useless and convulsive and irregular as those of drunkards" (*D.m.l.* 103 and 105). How close Harvey is here to Hughlings Jackson, who saw delirium and drunkenness as paralytic phenomena.[12] From these observations Harvey reached the following general conclusion: "It is one thing for a muscle to be contracted and moved, and another for it by regulated contractions and relaxations to perform any movement, such as progression or prehension. The muscles or organs of motion, when affected with spasms or convulsions from an irritating cause, are assuredly moved no otherwise than the decapitated cock or hen, which is agitated with many convulsive movements of its legs and wings, but all confused and without a purpose, because the controlling power of the brain has been taken away: common sensation has disappeared, under the controlling influence of which these motions were formerly co-ordinated to progression by walking or to flight" (*D.g.* 433).

He also recognized, however, that consciousness might play a large or small part in the control of the same movement. Thus, he said: "Embryos and animals at first walk delicately and practise the discipline of local movement just as a man who is learning to play upon the lute is always guarding against mistakes; their gait is vacillating, ambling paces" (*D.m.l.* 105). On the other hand, there is such a thing as "playing on the lute without being conscious [of the movements of the fingers]" (*D.m.l.* 41).

Sensation and Perception

Harvey had little to add to the ideas of the role of the peripheral nerves in sensation current in his day. Sensory and motor impulses were alike conceived as centripetal. There is, however, a hint of the afferent impulse in the following passage. Harvey asks whether the nerve which is sensitive is the same as that which is motive, or is it a different nerve. "And if it is the same nerve, is the movement in these nerves originated by the brain and does it return along with sensation to the brain like something which starts from the beginning and returns back to the beginning again, see Aristotle's triangle?" (*D.m.l.* 101.) Elsewhere he compares the nerve-impulse to the ebb and flow of the sea (*P.* 94c.). Harvey was clearly dissatisfied with the idea of a substantial "spirit" flowing in the nerves. His comment on this hypothesis is: "I think: the spirit does not travel in the nerves, but irradiates and becomes action, whence feeling and movement, like light in air" (*P.* 94c.). Later, in his "second disquisition to John Riolan,"[13] he completely rejects the idea of spirits as playing any part in physiology.

On the perception of movement he observes: "There is movement which we do not feel as that of the intestines. Nor do we feel the movement of the muscle but of the joints. Thus we perceive and we feel the fingers to move, but truly we neither perceive nor feel the movement of the muscles which are in the elbow" (*D.m.l.* 45). This view has only recently been established as physiologically correct.

When he considers perception, Harvey enters the sphere of psycho-physiology. "We have," he says, "consciousness in ourselves of five principal senses, by which we judge of external objects; but we do not feel with the same sense by means of which we are conscious that we feel—seeing with our eyes, we still do not know by them what we see, but by another sense or sensitive organ, namely the internal common sensation or common sensorium, by which we examine those things that reach us through each of the external sensoria, and distinguish that which is white from that which is sweet or hard. Now this sensorium commune to which the species or impressions of all the external instruments of sensation are referred, is obviously the brain, which along with its nerves and the external organs annexed, is held and esteemed to be the adequate instrument of a sensation. And this brain is like a sensitive root to which a variety of fibres tend, one of which sees, another hears, a third touches, and a fourth and a fifth smell and taste" (*D.g.* 432).

Harvey accepted Aristotle's view of the formation of universals from sensations. "Universals," he wrote, "are first imbibed from particulars by the senses and in so far are only known to us as an universal is a certain whole and indistinct thing, and a whole is known to us according to sense. For though in all knowledge we begin from sense, because, as the philosopher quoted (Aristotle) has it, sensible particulars are better known to sense, still the sensation itself is an universal thing. For, if you observe rightly, though in the external sense the object perceived is singular, as, for example, the colour which we call yellow in the eye, still when this impression comes to be made an abstraction, and to be judged rather than understood by the internal sensorium, it is an universal" (*D.g.* 155).

In discussing the stimulus to movement Harvey relies almost entirely upon Aristotle. "The living creature is moved by appetite or choice when some alteration has been set in motion on the occasion of sensation or imagination" (*D.m.l.* 35). But Harvey adds an idea of his own, for while Aristotle believed that appetite and the object of appetite cause movement when they themselves are moved, Harvey adds: "This is particularly true in the case of appetite, for it is by reason of an alteration which is set in motion that a living creature is made to have an appetite for this thing or for that" (*D.m.l.* 37). Harvey thought, moreover, that the pursuit of a desirable object or the avoidance of an unpleasant one was linked with some change in the body in the direction of heat or cold. This seems to have been the result of observation that changes of temperature in the body or its parts occur with changes of emotion, and also perhaps of the more general idea that heat and cold themselves symbolized positive and negative energy.

Anatomy and Functions of the Brain

Harvey's knowledge of the anatomy and functions of the brain is set out chiefly in the last part of the *Prelectiones*, the notes for his lectures on anatomy. The only published version of these is the transcription published by the College in 1886. Harvey's notes photographically reproduced in this volume are written in what Aubrey[14] calls his "very bad hand" in a mixture of his "very bad Latin"—to quote Aubrey again—and English, sometimes used, I suspect, when he did not know the Latin equivalent. To add to the reader's difficulties he introduces his own abbreviations,

and punctuation is often lacking. It is not surprising that the published transcription is not always accurate. I do not claim that my own translation is entirely so, but I have included only those passages which seem to me reasonably free from doubt. Harvey's account of the naked-eye anatomy of the brain is systematic, clear, and on the whole accurate as far as it goes. He begins with the skull, and debates many questions of interest with which I have not time to deal. He discusses facial appearances, and mentions the association of a small head with a fleshy face and long jaws like a horse (*P.* 88c.)—perhaps acromegaly.

He notes the two tables of the calvarium and that it varies in thickness "WH whence caution in trepanning one side being through before the other. Whence not when the brain swells." He describes two meninges, the dura and pia mater, including the arachnoid in the latter, and gives a detailed description of the dural sinuses. This leads him to a discussion of the pulsation of the brain, which some attributed to the sinuses. "Laurentius," says Harvey, "says that those who do not think so are mad. WH I am mad" (*P.* 90). Harvey's view is that the pulsation comes from "the arteries and spirits, consequently the whole brain looks like a quagmire." He notes that coughing makes the brain swell. He gives a good account of the cerebral ventricles, but is sceptical of the traditional attribution to them of mental faculties. "Is the substance of the brain or the ventricle the chief part? I have seen ventricles full of water" (*P.* 92c.). Those who attribute imagination and intellect to the ventricles "would put the soul, the divinest faculty in prison and mingle the highest things with excretions" (*P.* 93). "Memories, if functions of the brain, are in the substance, as conserving better" (*P.* 94).

Commenting on the division of the brain into right and left hemispheres, Harvey says that it is remarkable that a lesion of the right hemisphere should cause paralysis on the left side, and conversely (*P.* 91c.). His observations on neuropathology are scanty and often difficult to interpret. He was familiar with hydrocephalus and quotes a case of Dr. Argent's in which, he says, the whole brain had been absorbed and there was nothing left but meninges (*P.* 92c.). He notes the relationship between apoplexy and lesions in the neighbourhood of the ventricles, and describes his own observations in cases of apoplexy in which he has found a substance "like chopt brann, like a little Poridg" (*P.* 93)—perhaps the softening of infarction. He also mentions distension of the cerebral veins. Epilepsy, he says, is believed to originate in the region of the cerebral ventricles "either when an abundance of matter there acts as an irritant or, as others think, when the spirits contained there are too little agitated" (*P.* 93). We are still discussing whether constitutional epilepsy is a disturbance originating in the neighbourhood of the ventricles, and if so whether it is a manifestation of too much or too little nervous activity. "Convulsive movements," he says, "are occasioned by disease and are outside the senses and command of the soul and arise from an affection of the spirit" (*D.m.l.* 149); by which, of course, he means what we should now call the nerve impulse, and not the psyche.

Harvey as a Clinical Neurologist

Harvey's observations on patients suffering from nervous disease have to be gleaned chiefly from notes made in illustration of points of anatomy and physiology in his writings. He was familiar with changes in the size of the pupils, for he mentions Galen's observation that when one eye is shut the pupil of the other is seen to be dilated (*D.m.l.* 109). He also mentions constriction of the pupils (ibid. 69), and Galen's idea that the decussation of the optic chiasma is to prevent double vision. He noted that "if the nerve is compressed at the olecranon, two fingers become numb, if a nerve is compressed in the hip the whole leg becomes numb, and is deprived of sensation but not of movement" (D.m.l. 103). He gives a classification of gaits which is graphic but does not always enable them to be identified (*D.m.l.* 53). A gait like "a crane" may perhaps be a steppage gait. "Ambling Turk" and "trotting servile" may be descriptions of Parkinsonism. "Tripping on the toe, cork shoes" suggests spastic paraplegia, and "stamping on the feet" is still used to describe the gait in tabes. When he says that the obese "waddle like a puffin" (*P.* 7c.) he is probably recalling his visit to the Bass Rock, of which he gives the graphic description of a true bird-lover (*D.g.* 208).

The title of Chapter 19 of the *De motu locali animalium* is "Of the affections of muscles, or of the distorting of movement." The classification of these could at that time have little scientific basis, but Harvey's list contains some points of interest. Item 1 is "paresis: dead palsy"; item 2 is "tremor: shaking palsy." Item 3 is "convulsion," and here he differentiates epileptics, hysterics, and children. Item 4 covers "contraction of the limbs as of the legs in scurvy," and he also mentions "arching of the body backwards or forwards as in tetany." Other disorders mentioned are cramp resulting from excessive purging; "twinges, palpitation, convulsion from twitches accompanied by slight pain and pricking or by none, △WH particularly Mr. Rant's eye."

Harvey was obviously particularly interested in Mr. Rant's eyelid, which he mentions on several occasions. Mr. Rant appears to have suffered from either blepharospasm or facial myoclonia, for Harvey says: "In Rant's eyelids . . . there is contraction towards the centre" (*D.m.l.* 103).

He gives a good description of muscular fasciculation as "a pulsing or spirituous palpitation when either the skin or the muscle is first raised up and then depressed as in boiling or undulating movement." Finally he groups together "restlessness, persistent tossings, sleep-walking, harmful position in bed, mania, St. Vitus's dance" (*D.m.l.* 125).

These clinical observations are inevitably fragmentary. There is, however, one more detailed account of a neurological disorder, which better shows us Harvey as a clinical observer. This is the case of:

> "A young woman who during labour fell into so profound a state of coma that no remedies had power to rouse her, nor was she in fact able to swallow. When called to her, finding that injections and other ordinary remedies had been employed in vain, I dipped a feather in a powerful sternutatory, and passed it up the nostrils. Although the stupor was so profound that she could not sneeze, or be roused in any way, the effect was to excite convulsions throughout the body, beginning at the shoulders and gradually descending to the lower extremities. As often as I employed the stimulus labour advanced, until at last a strong and healthy child was born, without the consciousness of the mother, who still remained in a state of coma" (*D.g.* 534).

As a clinical observer, too, he was keenly interested in the facies and bodily conformation. He recognized three types of dwarf, commented on the association of obesity and somnolence in boys, and described exophthalmos, the eyes being in some patients prominent, moist, and relaxed, giving them a merciful and compassionate appearance associated with ready lacrimation.

Hunter and Macalpine[15] have discovered an account by Harvey of a patient with the symptoms of syringomyelia. Digby[16] quotes Harvey's description of this patient as evidence in favour of the view that there are separate nerves for sensation and movement. He was "a servant in the colledg of Physitians in London, whom the learned Harvey (one of his Masters) hath told me, was exceeding strong to labour, and very able to carry any necessary burthen, and to remove things dextrously, according to the occasion: and yet he was so voyd of feeling that he used to grind his handes against the walles, and against course lumber, when he was employed to rummage any; in so much, that they would runne with bloud, through grating of the skinne, without his feeling of what occasioned it." This must have interested Harvey as supporting his observation, which I have already quoted, that pressure on a nerve might abolish feeling but not movement.

That Harvey recognized that such loss of sensation might be hysterical is indicated by a patient described by Hollyer to Boyle[17] and also discussed by Hunter and Macalpine. This patient "was a Maid of about 18 Years of age, who, without the loss of motion, had so lost the sense of feeling in the external parts of her Body, that when he had, for tryal's sake, pinn'd her Handkerchief to her bare Neck, she went up and down with it so pinn'd, without having any sense of what he had done to her." Harvey, Boyle reports, went to see her out of curiosity, and thinking her disorder to be uterine, recommended marriage, by which "she was, according to his Prognostick, and to many Men's wonder, cur'd of that strange Disease."

Harvey in the *Prelectiones* mentions "Nan gunter etc. puto callum fecisse the mad woman pins in her arme" (*P.* 11c.). Nan, or Anne Gunter attracted considerable attention because she was suspected of being possessed by the Devil (Hunter and Macalpine.)[18] The Bishop of London referred her to the College for investigation. Dr. Wilkinson, Dr. Dunne, and Dr. Argent were appointed to do this (*Annals*, March 4, 1604/5). Unfortunately their decision is unknown, but King James I, who as the author of *Daemonologie*[19] was an expert on this subject, now intervened. He referred her for an opinion to Dr. Edward Jorden, a Fellow of the College, and then sent for her himself and by using psychological methods succeeded in curing her. And "the King giving her a Portion, she was afterwards married, being by this subtle artifice perfectly cured of her mimical Witchery"—an example of the royal touch in reverse. The fact that the King extracted from her a confession that she had only pretended to be a witch is not inconsistent with her having been a hysteric.

Harvey accepted the current view that hysteria was uterine in origin, but it would be a mistake to interpret this idea in an exclusively anatomical sense. Jorden, Harvey's older contemporary in the College, was the author of a book, called *A Briefe Discourse on a Disease called the Suffocation of the Mother*, which he dedicated to the President and Fellows. By this rather strange title he meant the uterine origin of hysteria, and his main thesis was that hysteria was not due to diabolical possession. Though he stressed the importance of uterine disorders, a substantial part of his book is devoted to showing that hysteria may have a psychological cause and respond to psychological treatment, for "the perturbations of the mind are often to blame for this and many other diseases."

Harvey's practice as an obstetrician and gynaecologist led him to lay some stress upon the uterus itself. He thought that a wide range of psychological disorders in women could be attributed to displacements of the uterus. Paradoxically, he reports two cases in which psychological disorders, in one melancholy and in the other hysterical symptoms of long standing, were cured by uterine prolapse, but remained well after he had replaced the womb (*D.g.* 542–3). He also describes two cases of pseudocyesis (*D.g.* 528–9): the symptoms, he says, depended on flatulence and fat. Also, however, he clearly recognized the psychosexual origin of some nervous disorders.

Psychosomatic medicine does not seem to have been very different in Harvey's day from our own.

> "Hence the stomach answering to the face
> the wasted face of the valetudinarian
> they feel an alteration after every article of diet
> they accumulate wind greatly on account of their size
> that is to say they generate it and cannot expel it
> on account of their weakness" (*P.* 28c.).

And here is a cry from the heart which will evoke many an echo to-day.

"There are many always complaining Lady Croft." (*P.* 19).

The "Ocular Philosopher"

I have shown you William Harvey as a neurologist, not to suggest that he contributed anything original to neurology, but to illuminate him as, in Sir Thomas Browne's[20] phrase, the "ocular philosopher," a great observer, alike of man and of nature, and a thinker whose intuition saw when traditional ideas were outmoded, even though he did not always know how they were to be replaced. And since his vision embraced the whole of life he was, as I began by saying, a comprehensive man. Let me in conclusion illustrate from his writings both his comprehensiveness and his prevision.

"Our common cock, whose pugnacious qualities are well known, as soon as he comes to his strength and is possessed of the faculty of engendering, is distinguished by his spurs, and ornamented with his comb and beautiful feathers by which he charms his mates to the rites of Venus, and is furnished for combat with other males, the subject of dispute being no empty or vainglorious matter, but the perpetuation of the stock in this line or that, as if nature had intended that he who could best defend himself and his should be preferred to others for the continuance of his kind" (*D.g.* 425). Now listen to Darwin.[21] "Thus the most vigorous females, which are the first to breed, will have the choice of many males and . . . will select those which are vigorous and well armed, and in other respects the most attractive . . . and this apparently has sufficed during a long course of generations to add not only to the strength and fighting powers of the males but likewise to their various ornaments or other attractions."

Now here is Harvey reflecting on the origin of the individual life, and seeking a parallel between the formation of the embryo and cerebral function. He asks: "whether the conception of the uterus be of the same nature or not with the conceptions of the brain, and fecundity be acquired in the same way as knowledge—a conclusion, in favour of which there is no lack of arguments; or, as motion and the animal operations, which we call appetites, derive their origin from the conceptions of the brain, may not the natural motions and the operations of the vegetative principle, and particularly generation, depend on the conception of the uterus?" (*P.* 372). This may sound a little like one of Sir Thomas Browne's fancies, but here is the answer of a present-day physicist:

"In the adult organism the information appears as macroscopical structural and functional complexity. In the germ cell it must evidently take the form of chemical complexity of the macro-molecules with which the genes are associated . . . Structural modification of protein molecules in the brain tissue . . . is equivalent to the prescribed storage of information in the chromosomes of the germ cell."[22]

The title "Ocular Philosopher" brings together the vision and the thought, so I venture to end with some lines which I wrote when I was President, suggested partly by the Harvey portrait in the library, and partly by Aubrey's words: "He did delight to be in the darke, and told me he could then best contemplate. He had a house heretofore at Combe, in Surrey, a good aire and prospect, where he had caves made in the earth, in which in summer time he delighted to meditate."

In cave like Plato's Harvey saw
Life's shadows moving in his mind,
And with its light dispersed the blind
Imposture of tradition's law.

Darkness and light dwell in those eyes,
Whose gaze discerned the heart's intent—
The blood's benign encirclement—
And learned in darkness to be wise.

I am most grateful to the Harveian Librarian, Sir Charles Dodds, the College Librarian, Mr. L. M. Payne, Dr. Gweneth Whitteridge, Dr. Charles Singer, and Mr. H. C. Gilson for help in the preparation of this Oration.

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FIELD TRIAL OF INFLUENZA VIRUS VACCINE IN PATIENTS WITH CHRONIC BRONCHITIS DURING THE WINTER 1957-8

REPORT BY THE JOINT WORKING PARTY OF THE MEDICAL RESEARCH COUNCIL'S COMMITTEE ON INFLUENZA AND OTHER RESPIRATORY VIRUS VACCINES AND OF THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION*

The acute exacerbations of the symptoms of bronchitis which occur in patients with chronic bronchitis and emphysema are a major cause of illnesses in general practice and are often responsible for sudden increases in demand for emergency admission to hospital (Abercrombie, 1956). Peaks of mortality from bronchitis are known to be related sometimes to environmental conditions such as smogs, but may also coincide with influenza epidemics (Reid, 1956). There is evidence both from serological studies and from the recovery of influenza viruses that these agents are sometimes the cause of infective exacerbations of illness in patients with chronic bronchitis (Stuart-Harris and Hanley, 1957). Yet the relative importance of influenza

*The planning subcommittee consisted of the following members: Dr. J. G. Scadding (chairman), Professor J. Crofton, Drs. C. M. Fletcher, J. C. McDonald, G. P. Maher-Loughnan, W. J. Martin, Professor C. H. Stuart-Harris, and Brigadier A. E. Richmond (Secretary).

The report was prepared by Brigadier A. E. Richmond and Dr. G. P. Maher-Loughnan.

The following chest clinics took part in this investigation: Ashford, Dr. P. E. Baldry; Birmingham, Drs. H. J. T. Ross and Edward Shieff; Bournemouth, Drs. A. T. Hendry and W. H. Tattershall; Bristol, Dr. A. T. M. Roberts; Camberwell, Dr. Kenneth Marsh and Miss D. B. Warren; Cambridge, Drs. L. Capper and M. J. Greenberg; Edmonton, Dr. V. Davies; Farnworth, Dr. J. L. Armour; Finchley, Dr. B. A. Butterworth; Hammersmith, The Staff of Hammersmith Hospital and Chest Clinic; Hastings, Dr. A. W. Anderson, Miss D. Jones, and Miss P. Willey; Headington, Dr. F. Ridehalgh, medical and lay staff; Ipswich, Dr. P. Embleton, Miss Ball (secretary), Miss D. Noakes (nurse); Islington, Dr. J. Wallace Craig and staff; Leeds C.C., Dr. G. F Edwards and staff of the Leeds Chest Clinic; Liverpool A, Drs. W. Gray and O. F. Thomas; Liverpool S, Dr. F. E. Crawley; Liverpool W, Dr. G. H. Murray; Middlesbrough, Dr. R. B. N. Wilsdon; Newcastle C.C., Dr. C. Verity; Newcastle R.I., Dr. A. G. Ogilvie; Paddington, doctors, health visitors, and clerical staff; Sheffield Royal, Professor C. H. Stuart-Harris; Sheffield, Dr. R. H. Townshend; Sheffield City General, Dr. C. S. Darke; Stockport, Dr. E. R. Smith; Stoke-on-Trent, Dr. F. Smith and Miss J. F. Cunningham (almoner); Sunderland, Drs. G. H. N. Bates and A. B. White; Swansea, Dr. T. W. Davies and all members of his staff; Uxbridge, Drs. S. L. O. Jackson, N. Rivers, and J. T. Nicol Roe; Willesden, Dr. C. H. C. Toussaint, Mrs. H. Jones (clerical); Edinburgh, 5, Dr. A. C. Douglas; Glasgow Southern General, Drs. R. J. Cuthbert, A. M. T. Drimmie, and K. R. Urquhart; Glasgow, Belvidere, Dr. R. Sinclair Kennedy; Glasgow, Knightswood, Dr. G. Johnston; Glasgow, Florence St., Dr. J. Cuthbert; Glasgow, Ruchill, Drs. G. W. Allan and A. W. Lees.

compared with other acute respiratory infections in the provocation of relapses is unknown.

It was considered reasonable, however, to conduct a trial of influenza vaccine in patients with chronic bronchitis because of the severity of influenza in such persons and with the hope that immunization, if successful, might reduce the need for admission to hospital during epidemics. A trial of the prophylactic effect of influenza virus vaccines similar to those held in Britain previously was therefore planned in 1957 by a joint working party of representatives of the M.R.C.'s Committee on Influenza and Other Respiratory Virus Vaccines and of the Research Committee of the British Tuberculosis Association.

Plans formed in April, 1957, were later altered because of the world-wide outbreak of Asian influenza. Though the epidemic in Britain occurred sooner than was expected, a trial took place which was a comparison in patients with chronic bronchitis of the effects of three vaccines—a monovalent vaccine made from the Asian virus, a polyvalent vaccine containing older influenza A viruses, and a vaccine containing influenza B virus.

Organization of the Trial

Recruitment and Inoculation

Participating chest clinics were asked to enrol cases of chronic bronchitis with or without bronchiectasis and cases of long-standing pulmonary tuberculosis with chronic bronchitis in which the tuberculosis had been quiescent for at least one year and which were not receiving chemotherapy. Patients with asthma were excluded, but cases of congestive heart failure secondary to chronic bronchitis were included. Patients who gave a history of intolerance to eggs were not accepted because of egg protein in the vaccines.

Allocation of each patient to one or other vaccine was made by means of a random order list, and the first batch of patients was assembled and inoculated as soon as could be arranged in September and early October, 1957. A second batch of patients was enrolled and inoculated with vaccines in the first week of December. Neither the patients nor their doctors knew the identity of the vaccines given.

At the time of inoculation each patient was questioned in regard to the occurrence of a productive cough for at least two months each winter over the previous three years, since this was the definition of chronic bronchitis employed for this trial. Questions concerning the degree of dyspnoea were asked to enable the patients to be graded in one of five categories of severity from none to dyspnoea on the slightest exertion (Fletcher, 1952).

The vaccines, which were prepared by Dr. F. Himmelweit at the Wright-Fleming Institute of Microbiology, consisted of:

Vaccine N: A polyvalent saline influenza A vaccine containing 10 mg. of aluminium phosphate and equal proportions of Swine, PR_8, and FM_1 totalling 20.000 haemagglutinating units (H.U.) per dose of 1 ml.

Vaccine O: An influenza B vaccine (1954) with 20.000 H.U. per dose of 1 ml. and 10 mg. of aluminium phosphate.

Vaccine S: An Asian type saline vaccine from the strain A/Singapore/1/57 with 20.000 H.U. per dose of 1 ml. and 10 mg. of aluminium phosphate.

Each volunteer received a 1-ml. dose of vaccine in a single dose by deep subcutaneous inoculation.

Follow-up and Record of Illnesses

The plan was to obtain as complete a record as possible of all illnesses subsequent to inoculation, with or without respiratory symptoms, so as to enable a diagnostic classification on clinical evidence. Each patient was provided with a stamped postcard which was to be completed and posted if he or she became ill enough to stay off work or to remain in bed for more than one day. On receipt of the card visits were made by a health visitor or, in the case of one clinic, by a medical officer. Those patients attending clinics regularly were questioned concerning their health between visits and those not attending regularly were given appointments at intervals up to the end of the trial in order to maintain their interest and contact with the clinic. An illness record sheet was completed by the health visitor or doctor in charge of the clinic, and this sheet contained details concerning symptoms, absence from work, and admission to hospital. If the patient had been admitted to hospital an illness record sheet was sent for completion by the doctor in charge. At each attendance at clinics details of any illness since the last visit were entered on the record sheet, and at the end of the trial in April, 1958, the records were completed or further details were requested from family doctors and hospitals.

During the trial it became evident that the arrangements for obtaining information about illnesses were not entirely satisfactory. It seemed that some patients who were unable to work or who were confined to bed had failed to return their postcards. It was also unfortunate that the information given on the record sheets did not indicate clearly which illnesses were to be regarded as recrudescences of bronchitis. Because of this, it was not possible to be certain that all such recrudescences were included in the final analysis, for some may have been grouped as "other illnesses."

Numbers of Volunteers and Categories

Table I shows that among the 42 participating clinics in England, Scotland, and Wales there were 2,542 volunteers (1,943 males and 599 females) whose records were complete and have been analysed. 59% of the males and 61% of the females were inoculated in September or October and the remainder in December.

TABLE I.—*Details Concerning the Inoculated Persons*

	Males		Females	
	No.	%	No.	%
Age in years:				
Under 20	3	0·2	4	0·7
20–	10	0·5	11	1·8
30–	92	4·7	87	14·5
40–	288	14·8	164	27·4
50–	776	39·9	166	27·7
60–	659	33·9	127	21·2
70 and over	49	2·5	21	3·5
Not stated	66	3·4	19	3·2
Total	1,943	100	599	100
Grade of dyspnoea:				
1. None	90	4·6	32	5·3
2. On hurrying on level or walking up slight hill	627	32·3	245	40·9
3. When walking on the level but not at own pace	628	32·3	191	31·9
4. Pause for breath on walking short distances on level	373	19·2	85	14·2
5. Breathless on undressing or talking	219	11·3	45	7·5
Not stated	6	0·3	1	0·2
Total	1,943	100	599	100

TABLE II.—*Attack-rate Per Cent. of Various Illnesses*

Group of Patients	No.	Vaccination Category	Influenza			Febrile Sore Throat			Stated Bronchitis			Other Illnesses			Total Illnesses		
			Polyvalent A	Virus B	Asian A	Polyvalent A	Virus B	Asian A	Polyvalent A	Virus B	Asian A	Polyvalent A	Virus B	Asian A	Polyvalent A	Virus B	Asian A
Males (1,943)	1,142	Inoculated September and October	16·8	18·6	7·9	1·3	1·8	1·8	32·4	29·2	35·7	24·9	34·6	28·6	75·4	84·2	74·0
	801	Inoculated December ..	6·0	7·3	5·8	2·2	1·5	2·7	24·3	36·0	24·7	20·2	18·2	21·6	52·8	62·9	54·8
Females (599)	368	Inoculated September and October	19·5	16·3	19·8	2·5	1·6	0·8	28·8	39·5	19·0	19·5	24·0	24·8	70·3	81·4	64·5
	231	Inoculated December ..	4·3	9·4	6·5	4·3	2·4	2·6	23·2	14·1	15·6	21·7	23·5	20·8	53·6	49·4	45·4

The distributions by age and by grade of dyspnoea show that the men were somewhat older and that more of them belonged to the severer grade of dyspnoea than the women.

Results

The results are presented in Tables II–V, which give details of the numbers of illnesses in separate clinical categories, of the severity of the illness, and of those patients who died during the progress of the trial.

Number of Illnesses

In Table II are listed separately the attack-rates of illnesses stated to have been influenza, febrile sore throat, bronchitis, or "other illnesses." The patients inoculated in September and October are separated from those inoculated in December because in most areas the Asian influenza epidemic occurred soon after the middle of September. Epidemiological and serological evidence suggests that cases of influenza continued to occur until the end of 1957 and in some areas during January or early February (McDonald, 1958).

Table II shows that the total number of illnesses did not differ materially between the groups of patients of either sex inoculated respectively in September and October or in December with the several vaccines. The bulk of these illnesses was described either as bronchitis or as other illnesses, and again these did not differ significantly in proportion according to the particular vaccine. Relatively few illnesses were described as being febrile sore throat, and the numbers recorded in the various groups of inoculated persons were similar.

The illnesses recorded as influenza were much commoner in both sexes in the patients inoculated in September and October than in those inoculated in December. The attack-rate in the men receiving the Asian vaccine in September and October was less than half the rate in those receiving either of the other vaccines, but there were no similar differences in the attack-rates among women. Because cases of influenza were occurring at the time of, or soon after, inoculation, the rates have been calculated separately for attacks occurring within eight days of inoculation and subsequently (Table III). This shows that the differences observed in the attack-rates among men inoculated in September and October applied to the illnesses occurring more than eight days after inoculation and were statistically significant; but there was no similar difference among women. The rates of influenza among persons of either sex inoculated in December also failed to show any significant difference attributable to the vaccines.

Duration of Illnesses

An analysis was made of the cases of illness causing the patient to be confined to bed in regard to diagnosis and to the average number of days in bed. There were no significant differences with febrile sore throat or other illness according to the vaccine used. Among the group of males vaccinated in September and October those receiving the Asian vaccine had a smaller number of days in bed. This was further examined by separating the illnesses occurring within the first eight days after inoculation from those at a later period. A shorter

TABLE III.—*Influenza Attack-rates*

	Inoculated in September and October		Inoculated in December	
	No. of Cases	Attack-rate (%)	No. of Cases	Attack-rate (%)
	Males			
1–8 days after inoculation:				
Polyvalent A vaccine ..	9	2·4	2	0·7
Virus B ,, ..	9	2·1	2	0·7
Asian A ,, ..	8	2·1	3	1·2
9 or more days after inoculation:				
Polyvalent A vaccine ..	54	14·8	14	5·3
Virus B ,, ..	64	16·9	18	6·6
Asian A ,, ..	22	5·9	11	4·3
Differences { Polyvalent A—Asian A	8·9±2·2 significant.			
Differences { Virus B—Asian A	11·0±2·3 ,,			
	Females			
1–8 days after inoculation:				
Polyvalent A vaccine ..	5	4·2	1	1·4
Virus B ,, ..	5	3·9	2	2·4
Asian A ,, ..	11	9·1	2	2·6
9 or more days after inoculation:				
Polyvalent A vaccine ..	17	15·0	2	2·9
Virus B ,, ..	16	12·9	6	7·2
Asian A ,, ..	13	11·8	3	4·0
Differences { Polyvalent A—Asian A	3·2±4·6 not significant.			
Differences { Virus B—Asian A	1·1±4·3 ,, ,,			

TABLE IV.—*Deaths Among Inoculated Persons*

Vaccine	September and October Inoculations		December Inoculations	
	Males	Females	Males	Females
Polyvalent A	21	—	5	—
Virus B	18	2	2	1
Asian A	14	1	6	0
Total	53	3	13	1

TABLE V.—*Deaths Stated to Have Followed Influenza*

Age	Sex	Grade of Dyspnoea	Date of Inoculation	Date of Onset of Influenza	No. of Days in Bed	Days Off Work	Date of Death
			Polyvalent A Vaccine				
53	M	3	30/9/57	26/10/57	14	14	10/11/57
57	M	4	27/9/57	10/10/57	18	Not working	5/11/57
69	M	4	4/10/57	20/10/57	11	Retired	1/11/57
60	M	5	20/9/57	26/11/57	6	14	9/12/57
			Virus B Vaccine				
63	M	3	24/9/57	5/10/57	1	3	10/12/57
50	M	4	16/9/57	4/11/57	8	14	23/2/58
			Asian A Vaccine				
None of the persons dying in this group had a prior attack of influenza.							

average number of days in bed was recorded in those receiving the Asian virus vaccine, but the differences between this group and the other two are not significant.

Deaths

66 males (3.4%) and 4 females (0.7%) died during the period of the trial. The causes of death included cor pulmonale or heart failure in 32 cases and pneumonia or bronchopneumonia in 12. There were 3 deaths from carcinoma of the lung and the remainder included chronic bronchitis (5), acute bronchitis (4), spontaneous pneumothorax (1), pulmonary embolism (1), coronary thrombosis (4), cerebral thrombosis (1), and suicide (1). No cause of death was stated in 9 patients. Tables IV and V show the distribution of these deaths according to the vaccine used and time of inoculation. There were fewer recorded deaths among the males inoculated in September and October in the Asian vaccine group, but the differences were not significant. None of the persons dying among those who received Asian vaccine was stated to have had a prior attack of influenza, compared with four who had been given the polyvalent vaccine and two the virus B vaccine. An analysis of the time of occurrence of the deaths according to the dates of inoculation failed to show any significant differences.

Discussion

This trial was handicapped initially because of the unexpectedly early outbreak of Asian influenza in Britain in September, 1957. Many of the patients were inoculated in areas where cases of influenza had already begun to occur, and insufficient time may have elapsed after inoculation for protection to have developed. Nevertheless the trial showed a definite protection against influenza in men inoculated in September and October, 1957, with the Asian vaccine but not in those receiving the polyvalent A vaccine. The order of protection was similar to that observed in the trials already reported in public schools, teachers' training colleges, and other miscellaneous centres (M.R.C., 1958). In these trials also, no protection was conferred by a polyvalent influenza A vaccine. This result differs from that obtained in U.S.A. by Gundelfinger and his colleagues (Commission on Influenza, 1957), who found that some protection against Asian influenza was produced by a polyvalent A vaccine not containing the Asian influenza virus.

The lack of protection against influenza in women with chronic bronchitis inoculated in September and October contrasted greatly with the results in the men. Though there were only 368 female patients compared with 1,142 men, the attack-rates from illnesses diagnosed as influenza was as high in those not given the Asian vaccine (16.3 and 19.5) as in the men (16.8 and 18.6). Moreover, the attack-rate for influenzal illnesses occurring more than eight days after inoculation was also as high in the women as in the men, so that the lack of protection afforded by the Asian vaccine was not due to a premature occurrence of the disease soon after inoculation.

The question of clinical diagnosis must be considered to be a possible explanation for the apparent lack of protection. Illnesses due to the influenza virus in persons suffering from chronic bronchitis may be recorded as exacerbations of bronchitis rather than as influenza. In fact, there were rather fewer attacks of bronchitis among women inoculated in September and October in those receiving the Asian vaccine than in the other two groups. Perhaps this difference was due to the fact that some of the attacks of bronchitis were due to the influenza virus, and, vice versa, that some of the attacks of influenza in the women inoculated in September and October were not caused by the Asian influenza virus. Yet, had such a diagnostic transference occurred, it is odd that it was met with only in women. A decision on this matter is impossible because of the fact, already stated, that the documentation was not strict enough to decide the nature of "other illness." Further, with only 110 women in the Asian vaccine group it may be that their difference from the men was more apparent than real.

There was no overall reduction morbidity amongst the patients with chronic bronchitis during the trial, and, though the duration of illness from influenza was somewhat reduced amongst the men inoculated in September and October, the difference was small. Under the conditions of this trial, therefore, influenza vaccination appeared to be of relatively slight benefit. Yet it must not be forgotten that the Asian influenza epidemic exhibited a somewhat different age-specific attack-rate from previous influenza A epidemics in that in some areas (Woodall *et al.*, 1958) illnesses were largely confined to children of school age and their family contacts. Also, the period of the year at which the peak occurred was in the autumn, and this may have helped to reduce the risk of chest complications.

The mortality seen during the progress of this trial was not chronologically related to the epidemic of influenza, though in a minority of cases influenza was blamed as the primary cause. Death from congestive failure often occurs many weeks after the initial deterioration, which may perhaps be the reason why inoculation with Asian influenza vaccine appeared to have little effect on the numbers of deaths occurring during the trial. Again it does not follow that the same consequence would be met with in the use of vaccine before an epidemic of influenza of a more normal seasonal character.

Summary

A trial is reported in which the relative effects of three influenza virus vaccines on groups of patients suffering from chronic bronchitis were studied.

Some patients were inoculated in September–October, 1957—somewhat late for the Asian wave of influenza—and others in December, 1957.

Though protection from influenza was provided in the earlier groups of male patients given "Asian" vaccine, female patients did not appear to be similarly safeguarded. Possible reasons for this were discussed.

No significant differences were observed between the attack-rates of bronchitis or other respiratory illnesses in the three inoculation groups. Finally, no significant differences in mortality were demonstrated between the several groups.

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INOCULATION OF HUMAN VOLUNTEERS WITH PARAINFLUENZA VIRUSES TYPES 1 AND 3 (HA 2 AND HA 1)

BY

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Chanock *et al.* (1958) have reported the isolation of two new myxoviruses which they named haemadsorption viruses type 1 and 2 (HA 1 and HA 2). They recovered the viruses from the respiratory secretions of small children with a variety of respiratory illnesses ranging from mild colds to pneumonia. They have confirmed these findings by further studies (Chanock *et al.*, 1959). Independently, one new virus (Cop 222) was isolated in Denmark, and several strains of another (Moss) were recovered in Sheffield, England. These were found to be serologically identical with HA 2 and HA 1 respectively (Birkum Petersen and von Magnus, 1958; Sutton *et al.*, 1959). HA 1 virus has recently been isolated in France also (Chany *et al.*, 1959).

The American workers found a significant association between virus recovery and respiratory disease. Because we had studied few cases and no control groups we had not been able to demonstrate such an association. We therefore wished to determine whether similar viruses which we had isolated in Europe were pathogenic for man by inoculating them to normal adult subjects living in strict isolation. In view of the recent statement of an international committee (Andrewes *et al.*, 1959) we shall refer to these viruses as parainfluenza viruses 1 (HA 2) and 3 (HA 1).

Methods

The volunteers were aged between 18 and 45 years. They were isolated in pairs at this unit, as described elsewhere (Andrewes, 1948). After a quarantine period of 2½ days the virus was administered as nasal drops in a volume of 1 ml. of Hanks's saline. Most volunteers also consented to have serum collected just before the inoculation was made and again about two weeks later, after they had left the unit. Throat swabs were collected two, four, and six days after inoculation. Until tested, each was stored at −60° C. in 3 ml. of 0.5% bovine plasma albumin in Hanks's saline.

Virus isolations and neutralization tests were performed in roller-tube cultures of human-embryo kidney or monkey kidney maintained in medium 199. The technique used was similar to that described by Chanock *et al.* (1958). Viruses from most volunteers were identified by neutralization or by haemagglutination inhibition tests with hyperimmune rabbit sera. For haemagglutination inhibition tests we used 4–8 units of virus and sera treated with cholera filtrate. Virus and serum were allowed to react for one hour before adding red cells, but otherwise the techniques were those employed with influenza viruses.

Complement-fixation tests were done in "perspex" haemagglutination trays, using 0.1-ml. volumes, 2 units of complement, and overnight fixation at 4° C. The antigens were fluids from monkey-kidney cultures infected with parainfluenza 1 and 3, standardized against human convalescent sera (kindly supplied by Dr. R. M. Chanock) and used in optimal dilutions. Neutralization tests were done by mixing a dilution containing about 100 infectious doses per 0.05 ml. of virus with equal volumes of serial dilutions of serum. About 20 minutes later 0.1 ml. of each dilution was inoculated to each of two monkey-kidney cultures. These were tested four or five days later by haemadsorption (Vogel and Shelokov, 1957), using human group O red cells. Virus infectivity titres and neutralization titres were expressed as interpolated 50% end-points. Recovery of virus or a fourfold or greater rise in antibody as measured by one or more techniques was taken to indicate infection of the subject.

Virus Strains.—Parainfluenza 1: We used Cop 222 isolated from a child in Copenhagen (Birkum Petersen and von Magnus, 1958) and serologically identical with HA 2. *Parainfluenza 3:* The Moss virus was isolated from a child in Sheffield, and is closely related to HA 1 (Sutton *et al.*, 1959). We also used a strain (K) of parainfluenza 3 virus isolated by one of us (M. S. P.) from a London child suffering from "febrile catarrh."

Results

Table I summarizes the outcome of the experiments in which volunteers received the Copenhagen 222 strain of parainfluenza 1 virus (Birkum Petersen and von Magnus, 1958). Eighteen subjects were given virus, and, in addition, three received inoculum in which virus had been neutralized by specific immune serum. Eight volunteers had detectable neutralizing antibody in the first serum specimen, but two of these became infected. Six subjects developed illnesses which, by the criteria used in this unit, were mild colds. All of these subjects were shown to be infected with the virus. Virus was isolated from the throats of nine volunteers in all. The positive specimens were those taken on the fourth or sixth day, about the time of onset of respiratory symptoms. All three volunteers who were infected by first-pass virus showed antibody rises. There was no antibody rise in the volunteers receiving fifth-passage virus, even in those from whom virus was isolated. No uninfected volunteers developed colds, but three who were infected had no symptoms, or those they had were not thought to amount to a significant cold. These

TABLE I.—*Effects of Inoculating Volunteers With a Danish Strain of Parainfluenza 1 Virus*

No. of Tissue-culture Passages of Inoculated Virus	Dose of Virus Given*	No. of Volunteers		No. of Infected Volunteers with Illness
		Infected†	Ill†	
1	15	4/5	3/5	3/4
2	1·5	2/2	1/2	1/2
5	15	0/6	0/6	0/0
5	150	3/5	2/5	2/3
5	0‡	0/3	0/3	0/0

* Expressed as tissue-culture infectious doses.
† Numerator = number of volunteers infected. Denominator = number inoculated.
‡ Same inoculum as in line above but mixed with rabbit immune serum against parainfluenza 1 virus.

results show that the virus infects man and apparently produces a mild illness of the upper respiratory tract or a subclinical infection. As little as 1.5 tissue-culture infectious doses initiated infection and caused symptoms.

Table II summarizes the results using the Moss and K strains of parainfluenza 3 virus. Sera collected before inoculation all neutralized Moss virus. Fifteen subjects were given the Moss virus and five developed illnesses. All those who became ill were infected with the virus, and one of those who remained well was infected. Virus was isolated from the throat of one volunteer from whom paired sera were not collected. There was a rise in antibody titre in the paired sera from five other volunteers when these were tested by one or more of the three methods used. Virus was recovered from three of these five volunteers. Virus was recovered from both volunteers receiving the K virus and both showed a rise in antibody titre. Fifteen TCD_{50} of these viruses failed to produce infection of the six volunteers used in the tests.

In the serological investigations of volunteers infected with types 1 and 3 virus, antibody rises were detected in nine cases by neutralization tests, in six cases by complement-fixation tests, and in three cases by haemagglutination inhibition tests. There were five cases in which an antibody rise was detected by only one method, but virus was recovered from the throat of each of these volunteers. Some of the combinations of laboratory results are shown in Table III, which also shows that some antibody responses would have been missed if we had not used a variety of tests.

TABLE II.—*Effects of Inoculating Volunteers With Two English Strains of Parainfluenza 3 Virus*

Strain and No. of Tissue-culture Passages of Virus Inoculated	Dose of Virus Given*	No. of Volunteers		No. of Infected Volunteers with Illness
		Infected†	Ill†	
Moss 5	150,000	3/4	3/4	3/3
,, 5	15,000	2/4	1/4	1/2
,, 5	1,500	1/4	1/4	1/1
,, 5	15	0/3	0/3	0/0
K 2	1,500	2/2	2/2	2/2
K 2	15	0/3	0/3	0/0

* Expressed as tissue-culture infectious doses.
† Numerator = number of volunteers infected. Denominator = number inoculated.

TABLE III.—*Representative Laboratory Results in Five Infected Volunteers*

Inoculum		Virus Isolations on Day			Homologous Antibody Titrated by		
Strain	Dose	2	4	6	Neutralization*	Haemagglutination Inhibition*	Complement Fixation*
Cop 222:							
1st pass.	15	0	+	+	<4/>16	64/64	5/160
2nd ,,	1·5	+	+	+	<4/<4	8/<8	<5/20
,, ,,	1·5	0	+	+	<4/<4	16/24	10/10
Moss ..	150,000	+	+	0	32/128	32/32	80/80
,, ..	15,000	0	0	0	16/64	<10/20	10/80

* The first figure represents the titre of serum collected before infection and the second of serum collected after infection.

TABLE IV.—*Summary of Symptoms Produced by Parainfluenza Viruses and by a Typical Common Cold Virus*

	Frequency of Symptoms and Signs in Illnesses Produced by			
	Parainfluenza			Cold Washings H.G.P.
	Type 1 Cop 222	Type 3 Moss	Type 3 K	
>4 handkerchiefs/day* ..	5	5	2	12
Mucopurulent nasal discharge	1	3	0	5
Nasal stuffiness	6	4	2	11
Sore throat	5	4	1	10
Cough	0	1	1	9
Temperature >99·2° F. (>37·3° C.)	1	0	1	0
Incubation period (days) ..	1–7 (av. 4)	3–6 (av. 4)	3 and 4 (av. 3·5)	1–3 (av. 2·1)
Total no. of cases	6	5	2	12

* Indicates that volunteers used more than four paper handkerchiefs a day—an index of increased nasal secretion.

Symptoms and Signs in Infected Volunteers

Throughout these trials the clinical observer (M. L. B.) was unaware of the type of virus being used, and his impression was that, with one exception, the illnesses produced by these parainfluenza viruses fell within the range of illnesses produced by a "typical" cold virus—that is, nasal washings from an adult with afebrile coryza not transmissible to cultures (see Roden, 1958). This clinical impression was supported by an analysis summarized in Table IV. However, the incubation periods of colds produced by parainfluenza were longer than those in "typical" colds. In addition, one volunteer who received 1,500 TCD_{50} of the second tissue-culture passage of the K strain of parainfluenza type 3 virus developed a fever lasting four days (maximum temperature 101° F.; 38.3° C.), muscular aching, headache, coryza, cough, and a little sputum. She had, in short, clinical influenza, though her partner had a mild cold.

Discussion

We considered the possibility that the colds experienced by our volunteers were produced by a common-cold virus carried over from the washings from which the parainfluenza viruses were first isolated. It seemed unlikely that such a virus would survive five passages in monkey-kidney cultures and cause colds, since unpublished experiments designed to show this with a "pedigree" cold have been unsuccessful. The colds might have been produced by a non-cytopathic monkey-kidney virus which our tests might not have shown up. However, since the only volunteers to be ill had laboratory evidence of infection with parainfluenza viruses, and since no illness was found in volunteers who were not infected, we conclude that the parainfluenza viruses caused the illnesses.

The conclusion that our Danish parainfluenza 1 strain produced cold-like illnesses in adults is independent confirmation of the findings of Reichelderfer *et al.* (1958) in the U.S.A. We know of no previous published report that parainfluenza 3 strains cause illness in human volunteers, but our results with the Moss strain of parainfluenza 3 are very similar to those with parainfluenza 1. These experiments seem to fulfil the third clause of Koch's postulates for these viruses as causes of respiratory disease in man. It seems that parainfluenza 3 virus can cause colds and an influenza-like illness in adult volunteers, and Chanock *et al.* (1959) have impressive evidence that it may be concerned in mild and severe acute respiratory disease in children. Adults inoculated with parainfluenza 1 developed only colds, but this virus has recently been recovered in Ireland from an adult with an influenza-like illness (Meenan and Clark, personal communication). In contrast with these results, we have, in unpublished experiments, failed to produce illnesses like the typical common cold by inoculating Echo viruses (types 11 and 20) obtained from children with febrile respiratory infections.

We should also emphasize that we have failed to isolate parainfluenza, or any other known virus, from

washings containing typical pedigree cold viruses such as H.G.P. (Table III). We therefore feel that it has yet to be proved that parainfluenza viruses can under natural conditions produce a common-cold-like disease in adults.

Summary

Eighteen human volunteers were inoculated intranasally with various doses of a strain of parainfluenza 1 virus. Nine became infected, and six of these developed illnesses resembling the common cold.

Twenty volunteers received parainfluenza 3 virus. Eight became infected, of whom six developed cold-like illnesses, one had an illness like influenza, and one remained well. The colds produced were clinically indistinguishable from those occurring after instillation of washings containing a cold virus, but the incubation period was longer in the parainfluenza virus infections.

We wish to thank the volunteers whose willing and conscientious help made these experiments possible, Dr. C. H. Andrewes for his interest and help in the clinical assessment of the volunteers, and Miss J. B. Macdonald, S.R.N., and Miss S. Witt for other assistance. The monkey-kidney tissue and medium 199 used were kindly supplied by the Medical Research Council Laboratories at Holly Hill, Hampstead.

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The Planning Committee of the Royal Commonwealth Society for the Blind was appointed in the winter of 1956 to "review the principles underlying the Society's present activities and to advise on the principles which should govern the next phase of development," and they have now summarized their recommendations in a report entitled *The Next Five Years*. In drawing up the Society's medical programme, the Committee were advised by the Society's panel of medical consultants, under the chairmanship of Sir Stewart Duke-Elder, who recommended that the Society should offer to undertake field trials, probably in Africa, following on the isolation of the trachoma virus; that it should award medical scholarships, make grants to individual investigators, and finance a mobile eye institute staffed by a medical orderly to bring drugs against conjunctivitis to Kenya villages. The importance of medical work in the Society's programme, say the Committee, is underlined by the fact that at least two thirds of the blindness in the Commonwealth is preventable, and that present facilities for research, prevention, and treatment are wholly inadequate. The Society's funds should be channelled into a few well-defined schemes, such as those described, which can make a large impact on the problem, but it should not itself become involved in schemes which are so general that they require long-term action by Governments, or so specialized that they can be undertaken effectively only by an organization exclusively devoted to medical work.

ANTIBODIES TO HAEMOPHILUS INFLUENZAE IN CHRONIC BRONCHITIS

BY

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The association of *Haemophilus influenzae* with respiratory disease other than epidemic influenza was recognized quite early (Kretz, 1897) but tended to be overlooked, particularly after the 1918 influenza pandemic. The shift of emphasis in the next few years to the influenza virus increased the neglect of the bacillus. Writing about chronic bronchitis, Marshall (1931) stressed the importance of exogenous infection by various organisms but made no mention whatever of *H. influenzae*. Mulder (1938) pointed out the frequency with which *H. influenzae* could be isolated from the sputum of patients with chronic bronchitis, and with the recent development of interest in this disease his results have been confirmed and extended (Mulder, 1956; May, 1958).

Several kinds of evidence demonstrate the closeness of the relation between chronic bronchitis and *H. influenzae*. It is the organism most commonly found in the sputum in this condition (Mulder, 1956), and is often present in pure or almost pure culture. If swabs are taken direct from the bronchi, so avoiding contamination with throat organisms, this predominance becomes even more marked (Brumfitt, Willoughby, and Bromley, 1957). Positive cultures are more common in patients with purulent than in those with mucoid sputum (May, 1958). Nevertheless the exact significance of *H. influenzae* in chronic bronchitis, and more particularly in the acute exacerbations of chronic bronchitis, remains uncertain. It was thought worth while examining the antibody response to *H. influenzae* in various stages of the disease to see whether further information on this point could be obtained.

Transient specific agglutinins to the autogenous strains of *H. influenzae* have been described in influenzal pneumonia (Wilson, Dunn, and Blair, 1924) and in bronchopneumonia (Humphrey and Joules, 1946). Wood, Buddingh, and Abberger (1954), using a slide-agglutination technique, showed a rise in titre lasting two to three weeks in 46 out of 51 infants with acute bronchiolitis. The titre was not related to the duration or severity of the disease. This problem differed from that of chronic bronchitis as all 32 strains of *H. influenzae* isolated belonged to one or other of Pittman's types. Similarly the extensive work on the immunology of *H. influenzae* meningitis is largely concerned with specific capsular polysaccharide antigens. The more relevant work of Faunce (see May, 1958) is discussed below.

Most respiratory strains of *H. influenzae* do not belong to specific Pittman types, but show marked antigenic heterogeneity (Wilson and Miles, 1955). Because of this, in all the agglutination reactions so far mentioned the patient's serum has been tested against his own strain of *H. influenzae*. In the present work all sera have been tested against extracts of *H. influenzae* prepared as described by Tunevall (1953) and shown by him to contain species-specific antigens common to all strains of *H. influenzae*.

By the use of tanned sheep red cells coated with such extracts, antibodies have been looked for and estimated

in sera from patients with chronic bronchitis in both quiescent and active phases of the disease, from patients with non-infected asthma, and from controls with no respiratory disease.

Methods

Preparation of H. influenzae extract (modified from Tunevall, 1953).—A freshly isolated respiratory strain of *H. influenzae* grown on boiled blood-agar was harvested after eight hours into 1% sodium carbonate. After one hour at room temperature the residue was removed by centrifugation and the supernatant dialysed against running tap-water for 24 hours. The opalescent viscid solution was then centrifuged again and the supernatant, with merthiolate to a final concentration of 1/10,000, was stored at 4° C.

Extracts from three respiratory strains were used.

Nature of the Antigenic Extract.—The three extracts used contained 2, 1.9, and 1.2 mg. dry wt./ml., of which approximately 3% was carbohydrate (anthrone method) and 66% protein (Folin–Ciocalteau method). (I am indebted to Dr. C. Jenkin for the protein estimations.)

Preparation of Standard Antibody.—Three rabbits were each given two injections, four weeks apart, of 2 ml. (2 mg. dry wt./ml.) of an extract, prepared as described above, mixed with 2 ml. of incomplete Freund's adjuvant (Bayol F and arlacel A only). The rabbits were bled four weeks after the second injection and the sera pooled.

Tanning and Sensitization of Sheep Red Cells.—Two to 14-day-old sheep red cells in Alsevers solution (supplied by the Serum Research Institute, Carshalton) were treated as described by Boyden (1951) except that dilutions of *H. influenzae* extract were used as the antigen and that all procedures were carried out at room temperature instead of at 37° C.

Antigen Titration.—The dilution of antigen required was determined by a preliminary titration repeated weekly for each batch of sheep cells. The final dilution used was such as to give the standard rabbit antiserum a titre of 1/32,000, and was usually in the range 0.06–0.12 mg. dry wt./ml. This is somewhat lower than the optimal concentrations given by Stavitsky (1954) for diphtheria toxoid =0.125 mg. and egg albumen =0.25 mg. *protein*/ml.

Antibody Titration.—Dilutions of patients' sera with 1% normal rabbit serum were tested against sensitized and unsensitized tanned cells. The standard antiserum was titrated with each batch to check the sensitivity. The specificity of positive sera was checked by inhibition with the antigen extract. Controls of sensitized and unsensitized tanned cells in 1% normal rabbit serum were always put up.

Patients Tested

Sera were obtained from 90 patients with chronic bronchitis, from 33 with asthma, and from 50 controls.

All those with bronchitis had suffered from chronic, usually productive, cough and breathlessness for at least two years. In addition they had, with varying frequency, acute infective episodes, particularly in winter. Some of them also wheezed, and would no doubt be classified by some physicians as having "asthmatic bronchitis" or "infective asthma." The justification for including them all under the one heading, bronchitis, is that they all had predominant cough and sputum.

The asthmatic group consisted of patients with paroxysmal attacks of wheezing and dyspnoea, often with milder but more prolonged wheezing between attacks. They had no sputum, or had small amounts of mucus mainly during attacks. Infective episodes were absent or rare.

The control sera came from patients in two wards who had no bronchitis or asthma, together with a miscellaneous collection of sera, sent to the laboratory for routine investigations, from patients with non-respiratory diseases. In order to improve the age-matching of the control and bronchitis groups, laboratory sera were used only if from patients over 50 years old.

Results

The age distribution of the three groups is shown in Table I. Most of the patients with bronchitis were over 40, while those with asthma were on the whole younger. The controls covered the age range of both but were mostly over 40.

56% of those with bronchitis, 58% of the controls, but only 33% of those with asthma were men. The sex distribution was approximately the same at all ages.

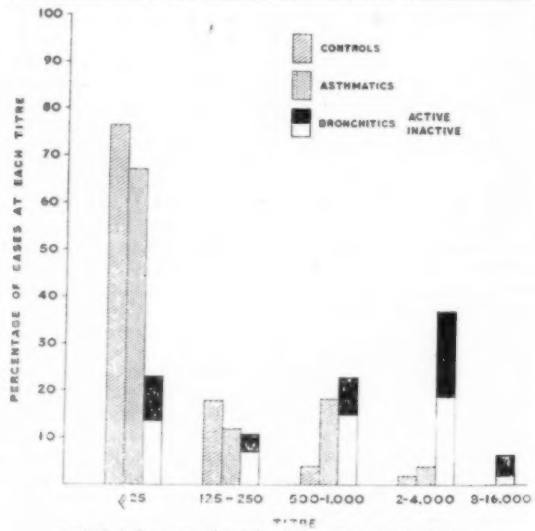
The distribution of antibody titres is given in Table II and the Chart. With a few exceptions the patients with

TABLE I.—*Age Distribution*

Age	Percentage at Each Age		
	Bronchitics	Asthmatics	Controls
0–19 years ..	0	12	2
20–39 ,, ..	11	33	6
40–59 ,, ..	51	52	54
60–79 ,, ..	38	3	38
No. in group ..	90	33	50

TABLE II.—*Anti-H. influenzae Titre in Three Groups of Patients*

Titre	No. of Patients		
	Bronchitics	Asthmatics	Controls
8,000–16,000 ..	5	0	0
2,000–4,000 ..	33	1	1
500–1,000 ..	21	6	2
125–250	10	4	9
<25	21	22	38
Total	90	33	50



Anti-H.-influenzae titres in three groups of patients.

asthma and the controls had very low titres, and the two groups were very similar. Most of the patients with bronchitis had high titres, 1/500 or more, though some were found over the whole scale. The difference between the patients with bronchitis and the controls is striking and significant.

The bronchitic group was then examined in more detail to see which factors, if any, were related to the antibody titre. No relation could be found between antibody titre and the age and sex of the patient or the duration of the disease.

Severity is difficult to measure objectively. A rough division was made into three grades—mild, moderate, and severe—based mainly on the amount of interference with work and normal living suffered by each patient. Patients in grade 1 were not off work from illness for more than three weeks a year and suffered little incapacity. Those in grade 3 were often in hospital or in bed at home and were unable to do their normal job. The rest were put in grade 2.

As always with such clinical classifications, grade 2 was rather large and covered too wide a range, but attempts at greater accuracy contained too great a subjective element to be of any value.

Using this crude measure of severity there was a slight but not statistically significant tendency for the more severe cases to have higher titres (Table III). When looked at individually conspicuous inconsistencies were found—both mild cases with high titres and, perhaps slightly more often, severe cases with low titres. It is not, of course, possible to say whether in fact they were severe because they had little antibody or mild because they had a lot.

Of the 90 patients with bronchitis 40 were tested two to three weeks after the onset of an acute infective attack in which *H. influenzae* was isolated from the sputum. The remaining 50 were tested during a quiescent phase. Comparison (Chart and Table IV) of antibody titres in the two groups shows no significant difference.

In 14 of the 40 patients with active infection paired sera were obtained, but in only one was there a significant rise over the period of two to three weeks (125–4,000). In two more there was a one-tube rise (1,000–2,000 and 2,000–4,000), while in one there was a one-tube fall (16,000–8,000). None of these changes can be regarded as significant.

TABLE III.—*Anti-H. influenzae Titre and Severity of Bronchitis*

Titre	Grade of Bronchitis		
	1	2	3
8,000–16,000 ..	0	3	2
2,000–4,000 ..	7	17	9
500–1,000 ..	5	10	6
125–250	2	8	0
<25	8	8	5
Total	22	46	22

TABLE IV.—*Anti-H. influenzae Titre in Active and Inactive Bronchitis*

Titre	Active	Inactive
8,000–16,000	3	2
2,000–4,000	16	17
500–1,000	8	13
125–250	4	6
<25	9	12
Total	40	50

In 10 patients further sera taken three to six months later all showed unchanged titres.

Discussion

The presence of antibody to *H. influenzae* to titres of 500 or more in 66% of patients with chronic bronchitis confirms the evidence already mentioned relating *H. influenzae* to this disease.

In the acute exacerbations of chronic bronchitis the position is less clear. If due to *H. influenzae* they might be followed by a rise in antibody titre. In the common more-prolonged states of active infection one might expect either a rise in antibody titre due to increased stimulation or possibly a fall if the antibody response were inadequate and circulating antibody were removed by increased antigen. The failure of the antibody titre to vary at all in acute attacks, while not supporting the haemophilus theory, does not disprove it. It is possible that absorption of antigen at the bronchial mucosa is poor, though Hers and Mulder (1953) have demonstrated *H. influenzae*, albeit in small numbers, between epithelial cells and occasionally deep to the basement membrane in cases of chronic bronchitis. The unchanged titre in some patients over periods of three to six months would fit with a steady slow absorption of antigen.

The work of Humphrey and Joules (1946) and of Wood *et al.* (1954) suggests that more rapid and more labile antibody responses can be detected with other, perhaps more superficial, antigens. In patients with chronic bronchitis Faunce (see May, 1958) found that an agglutinin titre of 1/20 or over against so-called rough or R strains of *H. influenzae* was more frequent among patients with purulent sputum than among those with mucoid sputum, but gave no figures of actual titres.

The relation between the antigens in sodium carbonate extracts as used in the present work and those responsible for the agglutination of Faunce's R organisms is unknown. Since the extracts were prepared from untypable respiratory strains they did not contain any specific polysaccharide. From Chen and Meyer's (1954) work using tanned red cells coated with protein and/or polysaccharide components of *Pasteurella pestis* it is probable that, under the conditions of sensitization used here (10 minutes at room temperature), protein would have been selectively adsorbed by the red cells and would have been the important antigen. However, some effect of the 3% carbohydrate present cannot entirely be excluded.

The present somewhat confused situation is unlikely to be clarified until much more is known about the markedly heterogeneous and poorly characterized antigens of respiratory strains of *H. influenzae*.

Summary

A method of detecting antibodies to *H. influenzae* by the agglutination of tanned red cells coated with a sodium carbonate extract of the organism is described.

With this method, antibodies in high titre (>500) have been found in 66% of patients with bronchitis compared with similar though never quite such high titres in 21% of asthmatic patients and 6% of controls.

Within the bronchitis group titres bore little or no relation to the duration or severity of the disease or to the presence of active infection.

The results confirm the close association of *H. influenzae* with chronic bronchitis but lend no support

to the theory that *H. influenzae* is responsible for the acute infective episodes which occur.

The need for further study of *H. influenzae* antigens is stressed.

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ACCIDENTAL INJECTION OF THIOPENTONE INTO ARTERIES

STUDIES OF PATHOLOGY AND TREATMENT

BY

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Thiopentone solution is sometimes injected accidentally into an artery in mistake for a vein during induction of anaesthesia. The clinical effects are well known. They range from gangrene and ischaemic contracture of muscles in the severe cases to minor degrees of anaesthesia of digits in the more fortunate patients. The clinical effects have been thoroughly described by Cohen in 1948, and by others whose publications are listed in the Bibliography. Uncertainty has existed about the nature of the vascular changes which follow the injection and which lead to the ischaemic end-results. This uncertainty has in turn led to some doubt on what treatment should be undertaken once the accident has happened.

Various factors have been suggested to explain the pathology. Prolonged arterial spasm has been postulated. It has also been suggested that the intimal layer of the artery is damaged and that thrombosis follows. The extreme alkalinity of thiopentone solution (usually about *p*H 10.9) has been blamed for these things. Widely differing treatments based on the uncertain nature of the pathology have been advocated or attempted. They have included the following measures:

(1) Injection into the damaged artery of a vasodilator drug. It has been advised that this be done immediately the accident has been discovered and, if possible, through the same needle without removing it. (2) The use of sympathetic or brachial-plexus block with local analgesic solution such as procaine (these measures being intended to relieve a postulated spasm of the injured artery). (3) Administration of anticoagulant drugs to prevent arterial thrombosis. (4) Arteriotomy and removal of clot from the vessel. (5) Arteriectomy: excision of a portion of the damaged vessel to relieve a theoretical reflex spasm of collateral branches.

Variable degrees of success have been reported after these measures, and it has been difficult to judge their efficacy under clinical conditions.

Laboratory Experiments

Investigations of the circulatory changes after intra-arterial thiopentone injections were for obvious reasons impossible in human subjects, so studies were undertaken in animals. The question of spasm was first investigated, employing a method similar to that described and used by Kinmonth and others in 1949, 1952, and 1957 in the rabbit and other animals. The intra-arterial injections were made into the femoral artery through a fine needle inserted just below the inguinal ligament. The needle-point was directed in a proximal direction as it would be under the clinical conditions of an accidental intra-arterial injection, and the needle was connected by a length of fine polyethylene tubing to a syringe to eliminate artifacts due to movement of the needle during injection. The artery was observed through a dissecting microscope a short distance below the site of injection, and changes in its diameter were measured with a micrometer eyepiece. Typical findings after an injection of 5% thiopentone are shown in Fig. 1.

There is a contraction of the vessel lasting about 30 seconds immediately after the injection of thiopentone. It is followed by a rapid return to the original diameter, after which a slight dilatation occurs for approximately one minute. On no occasion was any prolonged contraction observed nor anything at all resembling the spasm which follows mechanical trauma to an artery. Injections of buffered solution of alkalinity equal to that of thiopentone (0.1 M sodium carbonate/0.1 N hydrochloric acid, giving *p*H 10.9) produced no changes in the arterial diameter. This experiment was repeated many times with consistent results. On no occasion was anything other than transient contraction produced by thiopentone solutions, and alkaline solutions of equal *p*H never produced any change in arterial diameter.

The nature of the short-lived constriction and the ensuing vasodilatation after the thiopentone injection are of interest. They were also observed in animals where the femoral nerve had been divided and the femoral artery dissected free for a distance with the

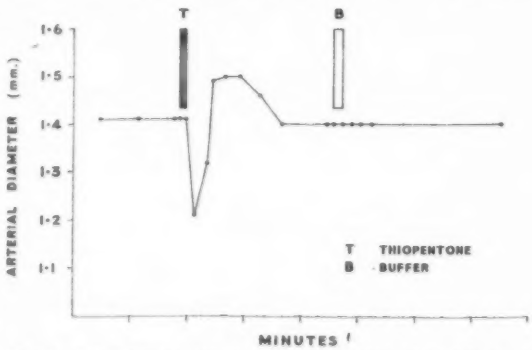

FIG. 1.—Injections into femoral artery of rabbits of (*a*) 0.5 ml. of 5% thiopentone at T, and (*b*) 0.3 ml. buffer solution of equal alkalinity (*p*H 10.9) at B.

object of denervating it. This suggests they were due to the direct effect of thiopentone on the vessel and not to a nervous reflex.

The period of vasoconstriction produced by the thiopentone injection is so short that it could not possibly explain the occurrence of necrosis after such an injection. Complete arrest of the circulation in the part by a tourniquet for much longer periods does not produce necrosis. Some cause other than vasoconstriction must be postulated to explain the occurrence of necrosis. That this might be so was also suggested by some experiments in which "ethamoline" (Glaxo) (Ethanolamine oleate *B.P.*) was injected into the femoral artery of the rabbit. No changes in diameter occurred after ethamoline injections, although thiopentone injections produced the same changes as those described above. Ethamoline is a substance regularly used to produce venous thrombosis in man, and can also be shown very readily to produce necrosis after intra-arterial injection in animals.

Production of Gangrene by Thiopentone Injection

The next step was to devise a method of intra-arterial injection of thiopentone in an experimental animal so that necrosis might be produced in such a way that it could be measured. The effects of countermeasures might then be tried, to see if the amount of necrosis could be reduced by treatment. After trials in different animals and at different anatomical sites it was found that injection into the central artery of the pinna of the rabbit fulfilled the requirements.

Technique

The rabbit was anaesthetized with intravenous pentobarbitone solution (26 mg./kg.). A light intestinal clamp was placed across the base of the pinna and a short incision made through the skin to expose the central artery, which was then injected retrogradely over a period of two minutes with thiopentone solution. The skin was closed with a few five-zero silk stitches. The clamp was used to stop bleeding around the artery and to facilitate the injection. It was also used to enhance the effect of the thiopentone, the dosage of which was limited because it was necessary to have the animal anaesthetized before the intra-arterial injection. It was found that an injection of 0.2 ml. of 10% thiopentone solution consistently produced massive gangrene of the pinna using this technique and keeping the clamp on the pinna for 15 minutes after the injection. This dose is roughly equivalent to an injection of 10 ml. of 10% thiopentone solution in a patient. Application of the clamp by itself for equivalent periods, or using this technique but injecting buffer solutions of equal alkalinity to the thiopentone, never produced any deleterious effects in the pinna.

The area of gangrene produced after three weeks by the standard technique just described is shown in Fig. 2. Some contraction usually occurred in and around the necrotic area, and so it was found that the area of tissue loss could be more accurately assessed at a later date, after the gangrenous area had separated, by measuring it in comparison with the contralateral control ear. The amount of tissue loss in another animal four weeks after injection is shown in Fig. 3. The average area of full-thickness loss of pinna was 14.5 sq. cm. in a series of 20 animals.

Effects of Countermeasures

Measures which might have been advocated as a form of treatment or which we thought might reduce the amount of tissue loss after intra-arterial thiopentone injection were next tried. They included intra-arterial injections of procaine solution, sympathetic denervation, and anticoagulant therapy with heparin.

1. Intra-arterial Injection of Procaine

Direct observation and measurement of the femoral artery of the rabbit by the method described above

FIG. 2.—Showing area of gangrene produced by standard technique after three weeks.

FIG. 3.—Tissue loss in another animal four weeks after injection.

showed that it was difficult to produce a prolonged vasodilatation of the artery by injecting dilator drugs such as procaine, tolazoline hydrochloride, or papaverine. The dilatation produced was invariably a transient one lasting no longer than five to ten minutes. Injection of procaine solution into an artery that has had thiopentone accidentally injected is, however, one of the main countermeasures advocated in clinical practice, and so it was decided to test whether it might have any protective effect after injection of thiopentone in the pinna of the rabbit. The thiopentone was injected with the standard technique described above. Procaine, 0.25 ml. of 4% solution, was then injected through the same needle and without removing it. The clamp was left upon the ear for the usual 15 minutes. This dose of 4% procaine is equivalent to some 5 to 10 ml. in a human patient. A series of 20 rabbits underwent this procedure. The average of the areas of tissue loss amounted to 15.2 sq. cm., which was approximately the same as that found in the untreated group, indicating that the procaine injections had no therapeutic effect.

2. Sympathetic Denervation

Removal of sympathetic vasomotor tone from the blood-vessels of the injured part is often advised as treatment for accidental intra-arterial injection of thiopentone. This might be supposed to give some protection by relief of a postulated prolonged arterial spasm. Our observations had failed to substantiate the occurrence of such a spasm, but sympathetic denervation might also be expected to exert a protective effect by increasing the flow of blood through the part, thereby discouraging clotting in damaged vessels. Blocking the vasoconstrictor pathways by injections of anaesthetic agents is uncertain in its effect and transient in duration, so sympathetic denervation of the pinna was effected surgically in a group of twenty rabbits immediately following the standard thiopentone injections. We are indebted to Dr. R. T. Grant of Guy's Hospital for advice on the method of doing this in the rabbit. The superior cervical ganglion and upper 1 in. (2.5 cm.) of chain was removed through an anterior incision. A short incision was then made behind the base of the pinna overlying the transverse process of the atlas, and the great and posterior auricular nerves were found and severed. Measurement of the tissue loss after the usual time showed it to be quite definitely less than in the untreated group, averaging 8.8 compared with 14.5 sq. cm. A typical example of an ear treated by this method is shown in Fig. 4.

FIG. 4. Typical example of rabbit's ear treated by sympathetic denervation.

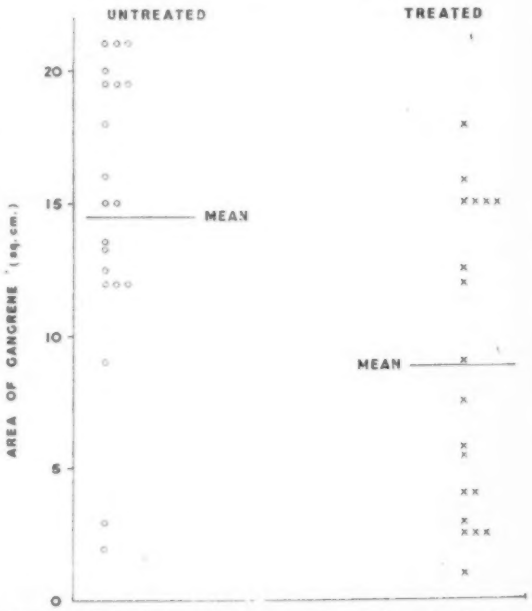

FIG. 5.—Effect of sympathectomy on area of tissue loss in pinna of rabbit after injection of thiopentone. Untreated animals on left had mean area of tissue loss of 14.5 sq. cm., animals treated by sympathectomy had mean tissue loss of 8.8 sq. cm.

There was a fairly wide scatter or variation in the area of gangrene which occurred in individual animals in both the treated and untreated groups, as may be seen in Fig. 5, but despite this there is a highly significant statistical difference.

3. Anticoagulant Therapy

The use of anticoagulant drugs might be expected to protect against ischaemic effects after intra-arterial injections of thiopentone by preventing thrombosis in the damaged vessels. The coumarol group of drugs were tried first, but were found to be difficult to administer and highly toxic in rabbits, and their use was not continued. Heparin was used instead, being given by intramuscular injection of 2,500 units/kg. every eight hours. Preliminary experiments showed that this high dosage was necessary in order to achieve a prolongation of the clotting-time of at least twice normal, lasting for seven to eight hours. A number of animals were lost from haemorrhage, usually at the site of intramuscular injection, but experience subsequently showed that it was necessary to maintain a high dosage for several days in order to produce a protective effect. In Table I the results are compared in a group of 15 animals in which full heparinization was effected for four days after intra-arterial thiopentone, compared with another group of 12 animals in which it was effected for only two days. The average areas of gangrene are 7.8 compared with 11.7 sq. cm.

TABLE I.—*Intra-arterial Thiopentone*

No. of Rabbits	Days of Full Heparinization	Av. Area Gangrene (sq. cm.)
15	4	7·8
12	2	11·7

TABLE II.—*Intra-arterial Thiopentone. Effect of Treatment*

Group	No. of Rabbits	Av. Area Gangrene (sq. cm.)
Untreated	20	14·5
Intra-arterial procaine	20	15·2
Sympathectomy	20	8·8
Heparin	30	9·2

The average area of tissue loss in 30 animals having full heparinization for two to four days after thiopentone amounted to 9.2 sq. cm. (see Table II). The first dose of heparin was injected into the central artery of the pinna immediately after removal of the clamp, subsequent doses being given intramuscularly every eight hours.

The protective effect compares well with that secured by sympathectomy but the mortality rate and practical difficulties in maintaining the treatment at an effective level were much greater.

Comparison of Different Protective Measures

The average areas of gangrene in four groups of animals in which the standard intra-arterial thiopentone injection had been made in the central artery of the pinna are shown in Table II. Intra-arterial procaine injections produced no effect, whereas both sympathetic denervation and heparinization had a definite protective effect and reduced the amount of gangrene after the thiopentone injections.

Prophylaxis

There is one possible prophylactic measure (other than the accepted methods of avoiding injection of an artery) which is subject to dispute and which is amenable to experimental test. This is the use of more dilute solutions of thiopentone for injection. The standard technique of intra-arterial injection was carried out in different groups of animals, varying the concentration of the thiopentone solution but using the same weight of drug. The results are shown in Table III.

The average area of gangrene proved to be inversely proportional to the strength of the solution of thiopentone used. When 2.5% solution was used for the injection the incidence of tissue loss was very low indeed. This relation of concentration to the extent of the necrosis ensuing was borne out by a review of published accounts of clinical cases (Table IV).

TABLE III.—*Intra-arterial Thiopentone. Effect of Varying Concentration*

Concentration of Thiopentone	No. of Rabbits	Average Area of Gangrene (sq. cm.)
10%	20	14·8
5%	10	10·4
2½%	10	0·15

TABLE IV.—*Intra-arterial Thiopentone. Incidence of Gangrene in Reported Cases*

Concentration of Thiopentone Used	No. of Cases	Cases with Gangrene
10%	10	6
5%	18	2
2½%	4	0
Unknown	2	0

The numbers in each group are small, but they support the belief that the more dilute solutions are safer.

Discussion

The sequence of events in an artery after an injection of thiopentone seems to be a momentary contraction followed by a short dilatation and return to the previous diameter. No prolonged spasm was observed in any artery. Later oedema and often redness and signs of inflammation develop in the affected part. This lasts for a variable time before occlusion of the circulation in the part occurs and it becomes cold. It was not possible to time the latter event in all animals, but it sometimes occurred as late as the third or fourth day. That the occlusion was due to thrombosis of the damaged artery was supported by evidence obtained from section and microscopy of the parts, but this evidence is not complete, as only a small number of animals were examined in this way, the majority being kept for assessment of the area of tissue loss.

Preservation of the injured tissues depends on maintaining the blood-flow through the part until recovery takes place. This may be done equally well by maintaining a brisk blood-flow by means of sympathectomy or by the use of heparin to prevent vascular thrombosis. Should heparin be used it might be wise to maintain the use of the drug for at least a week in view of reported clinical cases where the onset of ischaemia was delayed.

In a clinical case where thiopentone has been injected into an artery during induction of anaesthesia it would seem best to avoid going on with the intended operation and to place the patient on intensive heparin therapy. Should postponement of the operation be dangerous, then neurectomy of the sympathetic supply to the affected limb should be performed surgically.

Conclusions

There is no evidence that prolonged arterial spasm is the cause of the ischaemia following intra-arterial injection of thiopentone.

The ischaemia is caused by vascular occlusion due to damage by the thiopentone.

The injury is caused by the thiopentone itself and not by its alkalinity.

Sympathectomy or heparinization diminishes the ischaemic effects of injection.

Intra-arterial injections of vasodilator drugs are ineffective.

The danger of ischaemic changes after an intra-arterial injection is greater with strong than with dilute solutions of thiopentone.

We are grateful to Mr. M. P. Curwen, of St. Bartholomew's Hospital, for his help with statistical aspects of this work. Mr. S. M. Cohen has made freely available his considerable data on clinical aspects of the problem. Professor L. Young kindly supplied the buffered alkaline solutions. Mr. F. Scholefield and Miss N. Lowater have given technical assistance.

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GANGRENE OF FOREARM AFTER INTRAMUSCULAR CHLORPROMAZINE

BY

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Anaesthetists are aware of the catastrophes associated after the spread of accidental extravenous injection of piridoosal-diethazine (Sénèque and Huguenard, 1953), 1955). Recently, similar tragedies have been reported with hydroxydione (Schwarzkopf, 1958), and also after the spread of accidental extravenous injection of piridosal-diethazine (Sénèque and Huguenard, 1953), and promazine (Opinsky *et al.*, 1958). Gangrene due to an intramuscular premedicant injection is a less-known hazard, and appears to have been unreported.

Case Report

A woman aged 52, with a history of constitutional psychotic instability, accidentally sustained severe third-degree burns covering approximately 35% of her total body surface from the waist downwards.

After skin-grafting, the patient relapsed into acute mania, which made treatment difficult. During psychotherapeutic therapy the burnt areas were treated in enveloping plaster and were re-dressed as necessary under light general anaesthesia. Sepsis and decubitus ulceration took place under the plaster jacket, resulting in toxaemia and signs of renal damage. Blood transfusions and strenuous general measures were continuously necessary to maintain her general condition. After five months of treatment the patient had improved mentally and was alert and sensible, but her physical state had slowly depreciated and she had not tolerated repeated anaesthesia well. The dressings were latterly performed under light basal sedation. On the second occasion 50 mg. of chlorpromazine was ordered by intramuscular injection. The patient's legs and buttocks were covered with healing burns, and previous intravenous and intramuscular therapy had left residual soreness in both arms.

The injection (2 ml. of 2.5% solution), which was administered by a trained staff nurse, was given into the anterior aspect of the right biceps area, this being considered to be the best available site. No complaint of pain or discomfort was made by the patient at the time of injection, but twenty minutes later she remarked that her arm felt dead. On examination the arm was found to be flaccid, cold, and white. The brachial artery was pulsating in the upper arm, but from the site of injection downwards no circulation could be detected. From 1½ in. (3.8 cm.) above the elbow-joint to the finger-tips the limb appeared to be completely exsanguinated. Procaine (5%) was immediately infiltrated around the brachial artery at the injection level, and 25 mg. of tolazoline was administered intramuscularly. Neither measure had any obvious effect. Two and a half hours later a stellate ganglion and brachial plexus block was performed, using 1% lignocaine; this was followed after 15 minutes by Horner's syndrome, but by no alteration in the appearance of the arm. A few minutes later 40 mg. of papaverine in 20 ml. of water was injected into the subclavian artery, after which there appeared to be a slight flushing of the skin for an inch (2.5 cm.) or more below the previous line of exsanguination. Immediately after this procedure an intravenous injection of 15,000 units of heparin was given. Surgical exploration was undertaken eight hours from the time of the original intramuscular injection, the patient receiving light general anaesthesia with thiopentone, cyclopropane, nitrous oxide, and oxygen. The brachial artery, exposed in the upper arm, was found to be pulsating and healthy. At the level of the intramuscular injection there was some periarterial discoloration and haematoma formation, but no evidence that the artery had been punctured. From here downwards the vessel was contracted and immobile, and no blood could be aspirated therefrom. A 2% solution of papaverine was applied locally and 40 mg. of the drug in 20 ml. of water was injected into the artery at its lowermost normal point. These measures had no visible effect. Arteriotomy and arteriectomy were considered inadvisable.

Post-operatively, continuous heparinization was maintained and vasodilatation was encouraged by intramuscular tolazoline and by contralateral limb-heating. Support and gentle passive exercises were applied to the affected limb. In a few days there was a slight regression of the exsanguinated area on the radial side of the arm, and mottled bluish patches appeared around the surgical wound in the upper arm and spread into the forearm, particularly on the ventral aspect. The remainder of the forearm and hand remained bloodless, flaccid, and cold. Dry mummification took place in the finger-tips (Figs. 1 and 2). A line of separation eventually appeared, medially just below and laterally just above the elbow-joint. By the fifth day it was obvious that amputation of the forearm was inevitable, but in view of the patient's gradually depreciating condition conservative treatment was continued. The

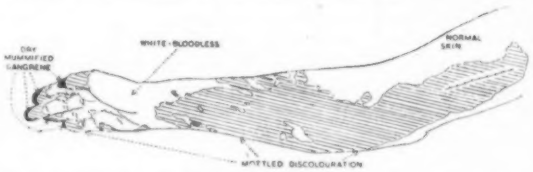

FIG. 1.—Ventral aspect of arm eight days after an intramuscular injection of chlorpromazine.

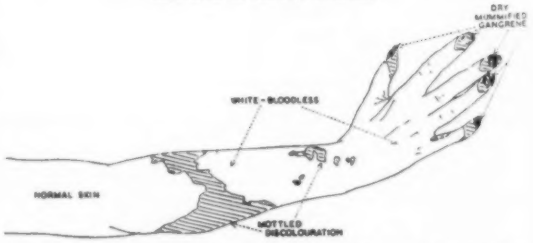

FIG. 2.—Dorsal aspect of arm eight days after an intramuscular injection of chlorpromazine.

patient died in an uraemic coma following renal failure two weeks after the intramuscular injection and five and a half months after her original injuries.

Pathology

At necropsy dry gangrene of the right hand, forearm, and elbow was confirmed, the brachial artery being thrombosed from the mid-upper arm downwards. Histologically the artery was occluded by an unorganized red thrombus. There was no evidence of intimal proliferation, and the elastic laminae and media appeared normal. The vessel was incompletely surrounded by an organizing haematoma involving the adventitia.

The pathological condition of the arm was considered to be one of several associated causes of death, the primary cause being septicaemia after burns.

Discussion

Arterial spasm, with ischaemic tissue necrosis as a secondary manifestation of sciatic-nerve injury, has been reported after intramuscular therapy (Lee and Stallworth, 1958), but otherwise it would seem that nerve injuries (Turner, 1920; Schmuttermeyer, 1936; Medical Protection Society, personal communication, 1958; Cohen personal communication, 1958), transient arterial spasm or local necrosis only (Gammel, 1927; Schönbauer, 1955; Harper, personal communication, 1958, Dundee, personal communication, 1958) are the main complications after intramuscular injections.

Chlorpromazine causes pain and irritation after injection (Dripps *et al.*, 1955; Simpson, 1955; Dundee, 1957) associated with an apparent inflammatory reaction. Thrombophlebitis, sterile abscess formation, and sloughing may occur (Harper, personal communication, 1958) occasionally necessitating skin-grafting (Dundee, personal communication, 1958).

The systemic vasodilatory effects of chlorpromazine are well established. Foster *et al.* (1954) showed, further, that in conscious subjects chlorpromazine caused a local vasodilatation (in doses of 1/80–1/6 mg./min. added to a brachial-artery infusion of 4 ml./min.). This effect was thought to be due either to blockage of the sympathetic vasoconstrictor nerve impulses in the vessel wall or to a direct effect on the arterial muscle. It is more than unexpected, therefore, that in this instance the drug produced intense arterial spasm. The patient did not complain of any symptoms at the time of injection, and at operation there was no local evidence of arterial puncture. Therefore the assumption remains that the periarterial injection caused an intense local irritation and an intractable reflex local and peripheral arteriolar spasm. A similar irritant effect on an adjacent artery after an inadvertent perivenous injection resulted in gangrene of the limb after other phenothiazine derivatives, piridosal-diethazine (Sénèque and Huguenard, 1953), and promazine (Opinsky *et al.*, 1958). The condition appears to have some resemblance to that known to follow high-altitude frostbite (Davis *et al.*, 1943) and in some instances of misplaced thiopentone injections (Cohen, 1948). The appearance of the arm and the absence of oedema suggested that the circulation was completely arrested in the forearm and that the main digital arteries became thrombosed within a very short time. Thereafter all treatment was useless.

The only beneficial effect appeared to follow the early intra-arterial injection of papaverine. Lack of precedence and first-hand experience of such cases led to some degree of reluctance to embark on surgical exploration, and this undoubtedly lessened the chances of success.

General anaesthesia of the type used is said to increase the peripheral circulation by 64%, but neither this nor the local operative measures applied resulted in any measurable effect in the limb.

It is impossible to dissociate completely the fatal outcome from the local condition of the limb. Renal and systemic effects from the adsorption of dead muscle have been shown to follow arterial thrombosis in the legs (Guthkelch, 1943; Bywaters and Stead, 1945), but in the absence of any effective circulation one would have expected these effects to be minimal.

While admitting that the choice of site and the technique of intramuscular injections are of major importance, there can be little argument that drugs with known irritant qualities should be administered in dilute solutions. Further, when no suitable muscle mass is available an alternative method of treatment should be instituted.

Summary

A unique case is reported in which the accidental periarterial intramuscular injection of chlorpromazine led to intractable local and peripheral arteriolar spasm, thrombosis, and eventual massive gangrene of the arm and forearm.

The particular considerations of the case are discussed.

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The New Zealand Cabinet has decided that, when a second medical school is built, it will be in Auckland. Mr. W. H. COCKER, chancellor of Auckland University, said he had been advised to this effect by the Prime Minister, Mr. WALTER NASH. No site has yet been decided on. The Senate of the New Zealand University appointed a committee in 1953 to recommend a site for a new medical school. It decided on Auckland, and since then it has been assumed that the school would be established there. But, because the Government had made no formal decision on the committee's recommendation, a deputation from Auckland University, including representatives of the Auckland Hospital Board, recently urged the Government to settle on Auckland as the site. The Senate has not fixed any date when the second medical school will be required (New Zealand Release No. A.19/59).

WERNER'S SYNDROME (PROGERIA OF THE ADULT)

FURTHER PATHOLOGICAL AND BIOCHEMICAL OBSERVATIONS

BY

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Clinical details of this case of Werner's syndrome have already been reported (Grant, 1957). Since then the opportunity has arisen to investigate more fully the steroid metabolism in this unusual condition and to report on the necropsy.

Results of various biochemical tests carried out on these patients in the past have been both conflicting and limited in scope, the only full study on adrenal steroids available being that of Bauer and Conn (1953). Post-mortem evidence, too, is scant. Out of 61 cases published to date, excluding the case here recorded, only the necropsy report by Oppenheimer and Kugel (1941) is available. Mavis Kelsey is quoted by Bauer and Conn (1953) as finding large adrenals with an adenoma in the cortex in necropsy. Oppenheimer and Kugel (1941) found a normal pituitary, adenomata of the adrenal and thyroid glands, and hyperactive parathyroids. Several theories of the cause have been advanced, all of which fail to explain fully the multiple facets of the syndrome. Indeed, the explanation would appear to be the problem of ageing itself.

Clinical Picture

The features of the syndrome, which vary slightly with different authors, may be summarized as follows:

1. *Premature Senility.*—This is a constant feature, starting at about 20 years of age and progressing with greying of the hair going on to baldness. Early cataracts and arteriosclerosis ensue, and the patient becomes senile between 30 and 40 years, with a piping, highly pitched voice and loss of teeth. Arterial calcification is marked.

2. *Pseudo-scleroderma.*—The skin and subcutaneous tissues atrophy, especially over the extremities, where the skin is very tight and thin and may cause contractures. Over points of pressure the tissues break down, with the appearance of ulcers. Associated occlusive vascular effects and chronic infection may lead to amputations.

3. *Characteristic Stature and Appearance.*—These patients are undersized owing to early cessation of growth. There is wasting with spindling, especially of the extremities, the nose is rather beak-like, and the features are gaunt and sharply defined. The abdomen and trunk do not share to the same extent in the wasting.

4. *Associated Endocrine Disturbances.*—Hypogonadism seems constant. Some patients have been described with mild hyperthyroidism and some with diabetes. Proptosis found in most of these patients is not due to hyperthyroidism. The condition may be confused with organic panhypopituitarism.

5. *Skeletal Disturbances.*—Arthritis, osteoporosis, and subcutaneous calcification are usual, and the latter also may lead to chronic ulcers.

6. *Hereditary Tendency.*—Since the original description, this feature has been noted by many authors, although a family history may be absent in individual cases.

The Role of Steroid Hormones and Liver Metabolism

It has been suggested by Bauer and Conn (1953) from their studies on the response to corticotrophin (A.C.T.H.) and oral compound S (17-hydroxy: 11-desoxycorticosterone) in a case of Werner's syndrome that the essential feature of this condition is a failure of the liver to detoxicate hydrocortisone.

Hydrocortisone is probably the active glucocorticoid and is normally removed from the circulation at a rapid rate (Peterson *et al.*, 1957). The details of how hydrocortisone is disposed of by the body are still obscure, although there is no doubt that the liver is of great importance. Cameron (1957) has reviewed in detail the present knowledge of the function of the liver in steroid metabolism. In liver disease hydrocortisone disappears from the circulation at a slower rate than normal, although related hydroxycorticoids—cortisone, corticosterone, and tetrahydrocortisone—disappear at normal rates, which are higher than that of hydrocortisone. Two main processes seem to be involved in the disposal of hydrocortisone—alteration in the steroid molecule, and conjugation of hydrocortisone and its metabolites, forming glucuronides. In the steroid molecule reduction takes place in ring A, and compounds of the tetrahydrocortisone, tetrahydrohydrocortisone, and dihydrocortisone type are produced. All these products appear in the urine as 17-hydroxycorticoids, mainly as conjugates, but 3–7% remain in the free form. Removal of the side chain from the hydrocortisone molecule leaves 17-ketosteroids, including weak androgens of the 11-β-hydroxaetiocholanolone type.

In a review of corticoid metabolism Jay Gold (1957) records that by chromatographic methods after cortisone infusion through a cirrhotic liver two abnormal steroids are found. These are 6-β-hydroxydeoxycorticosterone and allopregnane 17α,21-diol-3:11:20-trione, the latter being similar to cortisone except that the pregnene structure has been partially broken down. He summarizes the steps in hydrocortisone formation by the adrenal as follows: cholesterol—pregnenolone—progesterone—17-hydroxyprogesterone—compound S—hydrocortisone; and a similar scheme has been postulated by Hechter and Pincus (1954).

Bauer and Conn (1953) in an A.C.T.H. stimulation test gave 70 mg. in divided doses spread over six days to a patient with Werner's syndrome and produced a fall in circulating eosinophils, while low-control urinary 17-ketosteroids rose and then fell two days after stopping therapy. Formaldehydogenic steroids were at the upper level of normal (0.92–2.6 mg./day) during the control period and rose with A.C.T.H. to a maximum of 4.9 mg. Oral administration of 400 mg. of compound S produced a rise of 17-ketosteroids to 11.1 mg. on the first day and 18.3 mg. on the second day—a much smaller rise than expected—while formaldehydogenic steroids rose to 3 mg./24 hours after five days. The ordinary liver function tests were normal. The authors noted that the subnormal 17-ketosteroids and relatively elevated urinary formaldehydogenic

steroids with compound S administration were similar to the effects of liver dysfunction, and postulated an inability of the liver to convert compound S to 17-ketosteroids. Fajans, Louis, and Conn (1951) had studied the urinary excretion of 17-ketosteroids and formaldehydogenic steroids following administration of compound S both orally and intramuscularly. These authors had found an increase of four to six times in the urinary 17-ketosteroids without a corresponding increase in the formaldehydogenic steroids in two normal cases and in a case of Addison's disease. In a subject with cirrhosis, 400 mg. of compound S orally produced a rise of 17-ketosteroids of only 12 mg. as against the expected 35 mg. They concluded that the liver was responsible for the degradation of compound S to 17-ketosteroids. Bauer and Conn (1953) argued that if the liver in Werner's syndrome was unable to deal with compound S it could be similarly incapable of transforming hydrocortisone. If this process was of mild degree from birth and long-continued, excess hydrocortisone would produce an antianabolic effect, with failure to grow, atrophy of the tissues, and a tendency to diabetes instead of Cushing's syndrome. While A.C.T.H. gave clinical improvement in their patient they considered that it would eventually aggravate the condition.

Further Case Report and Method of Study

The patient, a man aged 62, was readmitted for further investigation on March 8, 1957. His general condition was similar to that previously described (Grant, 1957). In order to test further the validity of the theories referred to above, the following investigations were undertaken:

1. *A.C.T.H. Stimulation Test* (Fig. 1).—This standard test was carried out over a period of six days, involving two initial resting-days followed by four days of stimulation by a potent A.C.T.H. gel, 20 mg. b.d. intramuscularly. Urine specimens (24-hour) were measured and estimated for 17-ketosteroids and 17-ketogenic steroids by the modified Norymberski method (Appleby *et al.*, 1955).

2. *Cortisone "Utilization" Test.*—This was undertaken as in the A.C.T.H. stimulation test, with an initial period of two resting-days followed by oral cortisone acetate, 25 mg. q.i.d. for four days. Twenty-four-hour urine samples were similarly saved, measured, and estimated for 17-ketosteroids and 17-ketogenic steroids.

3. *Compound S "Utilization" Test.*—This was carried out in a similar manner to the above tests excepting that compound S, 100 mg. q.i.d., was given for one day only, after an initial rest period of two days. The results of this and of the cortisone "utilization" test are shown in Fig. 2.

4. *Additional Biochemical Investigations.*—These gave the following results. Urinary creatinine, 1,172 mg./24 hours; urinary creatin, 127 mg./24 hours; a urinary chromatogram showed a particularly raised excretion of taurine and slightly increased leucine and tyrosine; serum proteins totals, 6.0 and 7.0 g./100 ml. (albumin 3.6 and 3.6/100 ml., globulin 2.4 and 3.4/100 ml.); alkaline phosphatase, 19.3 and 23.8 K.A. units; serum calcium, 10.1 and 8.9 g./100 ml.; serum magnesium, 1.9 mg./100 ml; serum transaminase, 16 G.O. units; blood urea, 42 mg./100 ml.

Serum Electrolyte Levels in mEq/l. Taken on 10 Occasions Between May 11, 1956, and June 2, 1957. Specimen (b) Taken When Patient on Cortisone Acetate 100 mg. Daily and Specimen (g) When on A.C.T.H. gel 40 Units Daily

Specimens	a	b	c	d	e	f	g	h	i	j
Na	121	140	123	121	125	124	134	126	122	120
K	5·7	4·9	5·2	5·1	4·3	5·3	41	3·5	5·4	5·0
Cl	105	110	85	90	95	100	95	90	105	95
CO_2CP ..	24·8	25·5	26	26·8	27	27·7	31·3	29·4	34	26·8

Serum electrolytes were estimated on 10 separate occasions. The results are shown in the Table. At the time of taking specimen (b) the patient was on cortisone acetate, 25 mg. q.i.d.; and specimen (g) corresponds to a time when he was receiving A.C.T.H. gel, 20 units b.d. intramuscularly. The improvement in the serum sodium level is evident. It was further noted that while the patient was on test doses of A.C.T.H. he improved greatly, his appetite returned, and he volunteered that he felt stronger.

He was discharged at his own request on May 18, to be readmitted on June 13, in an extremely weak condition. Emaciation was extreme, but otherwise his condition showed little change. His temperature was 98.4° F. (37° C.), his pulse was in normal sinus rhythm at 78/minute, and his blood pressure was 90/50. He died suddenly on June 18, 1957.

Necropsy Findings

Post-mortem examination (Dr. B. Foley and Dr. J. E. Morison) was undertaken 21 hours after death. In view of the sparsity of previous port-mortem reports the findings are given below in some detail.

Macroscopic Examination.

The physical characteristics were striking, being those of extreme emaciation and senility, with complete loss of subcutaneous fat and absence of scalp and axillary hair, with only a few fine pubic hairs remaining. Numerous

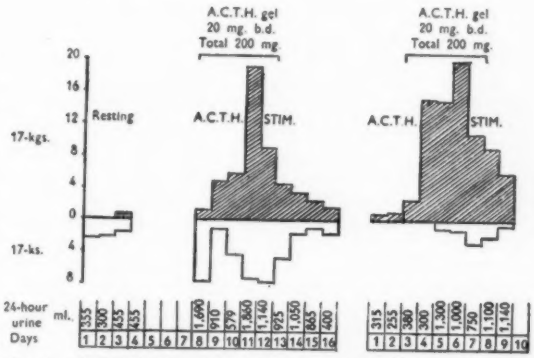

FIG. 1.—A.C.T.H. stimulation test on two occasions, with record of urinary output, of 17-ketogenic steroids (KGS), and of 17-ketosteroids (KS).

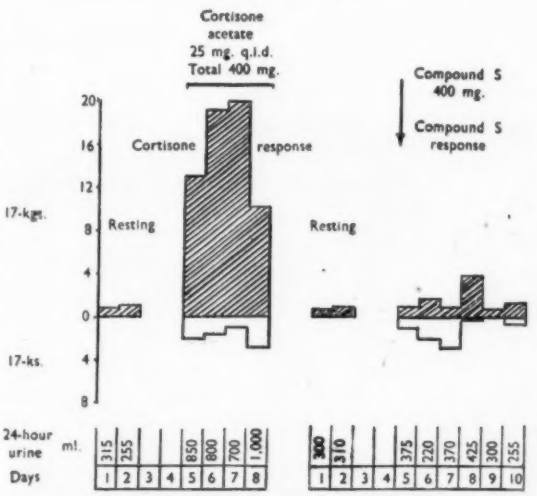

FIG. 2.—Cortisone and compound S "utilization" tests with record of urinary output, of 17-ketogenic steroids (KGS) and of 17-ketosteroids (KS).

septic lesions were noted in relation to bony prominences and joint surfaces. Both elbow-joints were dislocated and showed associated septic arthritis. The medial and lateral malleoli were ulcerated, as were the lateral borders of the feet and heels. The little toe of the left foot had sloughed away, leaving a raw infected surface. The fourth and fifth toes of the right foot had been amputated surgically. Post-mortem rigidity and lividity were present.

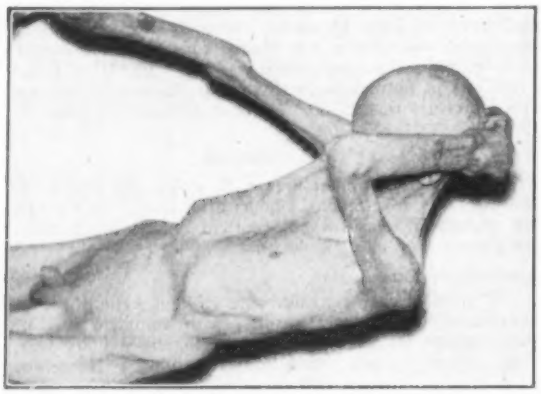

FIG. 3.—Physical characteristics of the patient.

The body cavities appeared normal. Pericardial fat was almost absent and the heart small, weighing only 175 g., compared with a normal weight of 300 g. There was no aortic valvular calcification, and the coronary arteries appeared normal apart from patchy calcification. The aorta showed some patchy atheroma of the arch and at its bifurcation, where there was also calcification. The lungs were consolidated in the posterior basal segments. The liver weighed 700 g. (normal 1,400–1,600 g.) and appeared atrophic on section. There was increased fibrosis of the splenic pulp, and the organ weighed only 60 g. (normal 150–200 g.) while the pancreas showed a normal lobular pattern and weighed only 60 g. The stomach, duodenum, and intestines were normal. The right adrenal weighed 2.75 g. and the left 3.4 g. (normal 5–6 g.). On section the lipoid content was decreased but not entirely absent. Perirenal fat was more or less absent and each kidney weighed 80 g. (average normal 150 g.). The surface was smooth and showed only a few scattered congenital cysts. On section the renal architecture was normal. The bladder was reduced in size and showed no trabeculation. The prostate

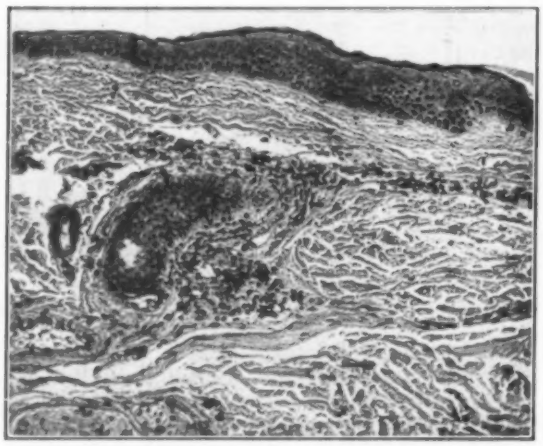

FIG. 4.—Skin of scalp. Atrophy of epithelium and skin appendages. (×125.)

was small (walnut-size) but otherwise normal. Both testes appeared small and atrophic, measuring 3.8 × 2 cm. The mucosa of the pharynx, oesophagus, and trachea appeared atrophic; the thyroid was very small and smooth on section; the parathyroid glands were not identified. The brain weighed 1,140 g. (average normal 1,400 g.). No atrophy of convolutions was noted.

Microscopical Examination.

The myocardium showed early "brown atrophy," the muscle bundles being generally smaller than normal, with an atrophic appearance; ischaemic fibrosis was evident, while the coronary arteries showed marked atheroma. The aortic cusp of the mitral valve was the seat of non-specific thickening with no vascularization. The lungs were emphysematous, and basal pneumonic consolidation, with areas of dense fibrosis and infiltration with plasma and small round cells, was present. Other cells had foamy cytoplasm, and fat stains were positive, suggesting lipoid pneumonia. In the liver the cells in the centre of lobules showed marked atrophy, but there was no acute necrotic change; marked glycogen and slight fat vacuolation of cells was seen. The spleen showed prominence of trabeculae with atrophy of the Malpighian corpuscles. The pancreas appeared normal apart from reduction in size of the islets. The adrenal tissue had an atrophic appearance, but lipoid was still present and a few small adenomata were

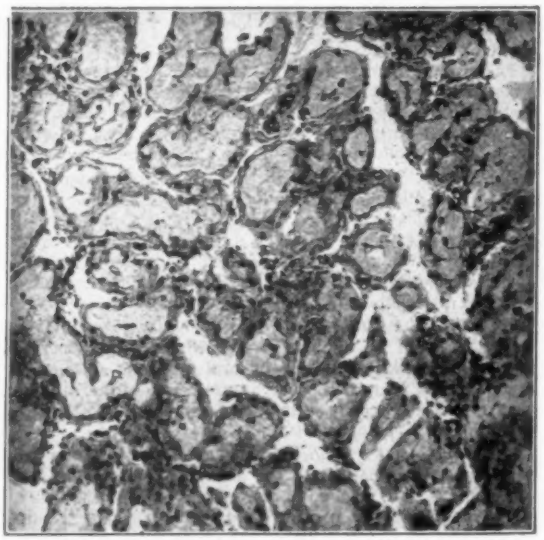

FIG. 5.—Testes. Complete atrophy of seminiferous tubules. (×75.)

seen. Apart from occasional glomerular calcification, the kidney was normal microscopically; nothing pathological was noted in the bladder. The prostate was very fibrous, the ducts were prominent, and the glandular system was very atrophic, all the glands being small, inactive, and lined by a single layer of epithelium. A granulomatous prostatitis was noted in relation to the prostatic urethra. The testes showed thickening of the tunica albuginea; the seminiferous tubules had no lining cells, were hyalinized, and were widely separated by oedema fluid. Occasional Leydig cells were seen. There was no evidence of spermatogenesis at any phase, and the whole picture was one of extreme generalized testicular atrophy. The thyroid and parathyroid glands had normal histological appearances. The trachea and oesophagus were the seat of subepithelial fibrosis, while the pharynx showed low-grade submucosal inflammatory reaction. The brain was microscopically normal apart from marked calcification of the smaller vessels. The pituitary gland, though very congested, was otherwise normal. Skin of the scalp, chest,

thigh, foot, arm, pubis, and shin were all examined. They showed the epidermis to be stretched and atrophic, while there was a thick fibrous layer in the dermis with loss of subcutaneous fat. Skin appendages, though present, were atrophic, and there was no attempt at hair growth in the scalp and only a few fine hairs on the pubis. In sections showing muscle, the bundles seemed to be irregular in size and shape and to have an increased proportion of fibrous tissue. The bone-marrow was atrophic and gelatinous, but showed no evidence of a gross disturbance.

Summary of Necropsy Findings

Death was due to "lipoid pneumonia." There was atrophy of the skin and skin appendages, with atrophy and patchy fibrosis of voluntary muscles. The trachea and oesophagus showed submucous fibrosis, while there was gross generalized atrophy of the testes and prostate. The adrenals were atrophic, showing much reduction in weight, thinning of the cortex, and the presence of multiple small adenomata. The liver was atrophic, being only half the normal average weight, while the heart and spleen were reduced in size to a lesser extent. The pituitary gland, though congested, had a normal cellular structure. The thyroid, the parathyroid glands, and the brain were essentially normal.

Discussion

Biochemical

In the patient under consideration the results of A.C.T.H. stimulation (Fig. 1) are compatible with hypopituitarism. Initial levels of 17-ketogenic steroids and 17-ketosteroids were low, but gains of 18–19 and three times the resting level respectively were observed on two separate tests—results which are not outside the limits one would expect with a hypoplastic adrenal responding to stimulation by the method employed. The daily volume of urine of this patient was consistently small (Figs. 1 and 2), and we have been impressed by this also in a case of dystrophia myotonica. It will be noted, too, that an increased daily volume of urine resulted from both A.C.T.H. stimulation and administration of oral cortisone acetate. This we interpret as improved excretion of a water load and would further support a state of hypopituitary function with adrenal hypoplasia. No similar diuresis occurred with compound S (Fig. 2), which is known to have no metabolic effects (Terry and London, 1950) (Pearson *et al.*, 1951). Functional pituitary deficiency is further suggested by the low level of gonadotrophins (4 mouse units/24 hours) and the relatively low blood-sugars in the glucose tolerance and in the insulin sensitivity tests reported previously (Grant, 1957). On test doses of A.C.T.H. and cortisone the serum sodium increased (Table I) and the patient improved physically.

After oral administration of 400 mg. of cortisone acetate over four days and 400 mg. of compound S the total recovery of metabolites was poor (Fig. 2), especially so in the latter, the maximum output of 17-ketosteroids being 2.8 mg./24 hours, while that for 17-ketogenic steroids was 3.8 mg./24 hours. Out of 400 mg. of compound S, only 6 mg. of 17-ketosteroids and 10.4 mg. of 17-ketogenic steroids were recovered over six days. The recovery rate after cortisone was 17 mg. and 63.0 mg. respectively, levels which are lower than expected but much better than after compound S. After administration of cortisone acetate 100 mg. a day in adrenalectomized patients, the expected recovery of 17-ketogenic steroids would be approximately 40 mg. a day (Moxham and Nabarro, 1956).

The Norymberski reaction is limited to estimation of the following side-chains at C_{17} (Butt, Kornel, and Morris, 1957):

CH_3	CH_2OH	CH_2OH
|	|	|
$CHOH$	CO	$CHOH$
|	|	|
COH	COH	COH
Pregnane Triols	Cortisone Hydrocortisone Tetrahydrocortisone	Cortol Cortolone

Adequate information about the recovery of compound S metabolites was unobtainable, but one would have expected this substance to behave as hydrocortisone and to be shown up by the Norymberski technique as an increase in 17-ketogenic steroids. Chemically these steroids are similar except at the 11 position, and compound S is a precursor of hydrocortisone. The possibility also arose that compound S as an inert substance might be metabolized in a manner different from cortisone, as proportions of the ketogenic and ketosteroid fractions were almost equal. The probability is, however, that the low renal output and consequent low excretion of total steroids, which was not improved by the relatively inert compound S, led to an accumulation of this substance in the body. More time was allowed for breakdown by the liver, and this would explain the appearance of a higher proportion of ketosteroids in the urine than was the case with active cortisone, which was rapidly excreted, mainly as 17-ketogenic steroid conjugates.

We have, further, to reconcile our results with those of Bauer and Conn (1953), who found a rise in formaldehydogenic steroids from a high normal resting level after administration of compound S and following A.C.T.H. stimulation. In both subjects the 17-ketosteroid output was lower than expected, and this was especially so in our case. We also found control levels of 17-ketogenic steroids to be lower than normal, a finding which would be hard to reconcile with an increased blood level and thus an increased urinary output of hydrocortisone. After A.C.T.H. and cortisone 17-ketogenic steroids increased much more than 17-ketosteroids, but were still subnormal. We do not feel that the relatively increased proportion of 17-ketogenic steroids to 17-ketosteroids in any way negates hypopituitarism. To confirm Bauer and Conn's hypothesis that the inability of the liver to break down hydrocortisone is the basic cause of Werner's syndrome the increase would need to be much more striking. Further, the much more equal proportions of the two steroids after compound S suggest that there was no impairment in breakdown of this substance to 17-ketosteroid, and by analogy of hydrocortisone to 17-ketosteroid, in our patient. These authors, however, were estimating substances of the α-ketol and non-reducing C_{20}-C_{21} α-glycol type as formaldehydogenic steroids (Daughaday, 1950), which include progesterone and other steroid products. It is generally agreed that the Norymberski technique is a more reliable procedure and has replaced estimation of formaldehydogenic steroids in the assessment of urinary hydrocortisone (Loraine, 1958). In this connexion it is also noteworthy that urine extracts contain substances other than steroids which yield formaldehyde on oxidation with periodic acid (Loraine, 1958), the presence of which might vitiate the result of estimations of formaldehydogenic steroids.

In our patient the urinary chromatogram showed a particularly raised excretion of taurine and slight excess

of leucine and tyrosine. Taurine has also been found as a trait in dystrophia myotonica by Lynas (1957), but further information on the clinical importance of this substance is scanty. Aminoaciduria might be taken as indicative of liver dysfunction, but it has been pointed out by Dent (1946) that gross aminoaciduria is encountered only in cases of massive liver necrosis or advanced cirrhosis, and taurine has not been noted following liver damage. The only other evidence of defective liver function is the slight reduction in serum albumin and the doubtfully significant increased excretion of 17-ketogenic steroids as against 17-ketosteroids previously discussed (Bauer and Conn, 1953).

The hereditary basis has again been stressed by Ellison and Pugh (1955), and, as they had found diabetes, skeletal decalcification, and impaired renal function with excess urinary aspartic acid, they considered the possibility in Werner's syndrome of a congenital innate defect of renal tubular reabsorption such as occurs in cystinosis and the Fanconi syndrome. They concluded, however, that there was no evidence for this concept. Our own case, too, showed no evidence of hyperchloraemic acidosis; in fact, electrolyte studies showed a pattern of salt depletion, and it was impossible to get the patient to take what might be regarded as adequate fluids orally.

Gross skeletal demineralization was found, but, apart from the increased alkaline phosphatase which has not been a constant feature in other cases described, there was no other suggestion of hyperparathyroidism. The original view of Oppenheimer and Kugel (1941) that increased parathyroid function was causal could not be confirmed in this as in other recorded cases.

Diabetes was not found in our subject, and is an inconstant finding in the literature, occurring in 11 cases out of 55 (Irwin and Ward, 1953). The metabolic disturbance which allows this to occur in the face of what appears to be pituitary underaction is as yet unexplained. It seems clear, however, that it is an effect of the syndrome rather than being in any way causative.

The increased figure for creatine in the presence of an almost normal urinary creatinine is probably due to both muscle-wasting and decreased tubular reabsorption, the latter in part due to the urinary excretion of other aminoacids (Thompson and King, 1957).

Pathological

The only previous post-mortem report is that of Oppenheimer and Kugel (1941). Here death was due to a primary hepatic carcinoma; in addition, multiple adenomata were found in the thyroid and adrenal glands, while the appearance of the parathyroid glands microscopically suggested increased activity. The prostate and testes were atrophic and the pituitary gland was entirely normal. The size of the organs was not in general reduced. A second patient described by the same authors died from a fibrosarcoma of the radius, while the second patient of Ellison and Pugh (1955) succumbed to a melanotic sarcoma. The incidence of malignancy in these patients is strikingly high. No evidence of malignant change was found in the case here presented, a few small adenomata only being evident in the adrenal gland. The steroid hormones are members of the cholanthrene-ring system and might have carcinogenic properties in a disordered state of cellular or steroid metabolism. Sugiura and Rhoads (1941) have shown the importance of a proper function of the intracellular enzyme system in the prevention of carcinoma of the liver. Such carcinogenic agents first produce destruction of cells, which is then followed by repair (Wolbach, 1937), the hyperplasia leading to malignancy. It is agreed also that malignancy is more common in the older patient.

In the case reported here the striking changes were found in the skin and subcutaneous structures—changes quite distinct from scleroderma (Thannhauser, 1945) or dermatomyositis. The main features were the atrophy of the epidermis with flattening of papillae, the almost complete absence of skin appendages, and the absence of oedema, arteritis, or lymphocytic infiltration. The elastic tissue was preserved in the deeper dermis, but in the immediate subepidermal area it was atrophic. No homogenization or sclerosis of collagen, seen in scleroderma, was noted. However, fibrosis in the submucosa of the trachea and oesophagus was similar in location to that affected by scleroderma.

The other remarkable feature in the necropsy was the general microsplanchnia with gross atrophy of the testes and prostate of a general type, similar to that described by Oppenheimer and Kugel (1941). The testicular atrophy differed in its diffuseness from that due to mumps or other infections. The adrenal glands, markedly atrophic and containing a few adenomata, were normal in cellular structure. Such adenomata are often found in post-mortem material. The pituitary gland, though congested, showed no definite abnormality. The pituitary was also normal in the case of Oppenheimer and Kugel (1941); and in the post-mortem accounts of progeria—a very comparable condition arising in the first or second year of life—the pituitary was also normal (Mitchell and Goltman, 1940) and there was no sign of a pluriglandular deficiency (Atkins, 1954). Microsplanchnia in progeria is similar to the findings here, but arteriosclerosis seems much more severe than in the present case, so that in the original necropsy of progeria (Gilford, 1897) the coronary arteries were concluded at 18 years of age.

The thyroid and parathyroid glands were normal in structure, in contrast to the findings in Oppenheimer and Kugel's (1941) case of active adenomata of these glands. The atrophic gelatinous bone-marrow afforded no clue to its causation. Serum calcium, phosphorus, alkaline phosphatase, and calcium-balance studies of Irwin and Ward (1953) have tended to rule out the likelihood of hyperparathyroidism being causative, as suggested by Oppenheimer and Kugel (1941). Indeed, Thannhauser (1945) records a personal communication from Oppenheimer in which he states that he no longer adheres to the opinion that the parathyroid gland is predominantly involved.

The liver, at half its normal weight, and the less-marked reduction in size of the heart and spleen also illustrate the microsplanchnia seen in the organs in general, excepting the brain. There seems no adequate explanation for this atrophy other than the effects of senescence.

The post-mortem findings here do not help particularly in the problem of aetiology. This is understandable, since it would appear that we are dealing with chemical pathology related to a genetically determined defect of cell enzymes of a general type. This view does not differ greatly from that so well put by Thannhauser as "multiple germ-plasm defects manifesting themselves in abiotrophic features of various organs at different periods of life."

Conclusions

In conclusion, the data considered above suggest a diffuse interference with cellular metabolism affecting

endocrine tissues as well as those of other structures, such as liver, kidney, skin, bone, etc. The post-mortem appearances noted were those of microsplanchnia comparable to a state of severe and premature senescence. The combination of the typical skin changes with gonadal atrophy is distinctive. The biochemical investigations strongly suggest functional hypopituitarism with adrenal hypofunction in this case. The multiple features and variation around a common and unforgettable clinical pattern cannot, however, be explained on a purely endocrine basis nor by the effects of reduced function of the liver or kidney alone. The clinical picture of the syndrome varies as a result of other factors superimposed on what is probably a single inherited trait. Modifications of the final syndrome may then be largely dictated by the relative degrees of hypofunction of various vital endocrine and metabolic organs and their resulting imbalances. The basic cellular disturbance as shown in the skin, hair, and body structure remains constant and determines the typical physical features. A deficiency of synthesis in one enzyme system vital to all cells may be responsible and so set in train the diverse pathological consequences encountered. This is probably an inherited heterozygous recessive character, and an analogy may perhaps be drawn to galactosaemia, Hartnup disease and Wilson's disease—conditions in which a tissue enzyme defect has been established.

Summary

The biochemical investigations and necropsy findings are described in a male patient of 62 years with Werner's syndrome. It is suggested that the condition is due to a generalized enzyme defect which causes premature senescence.

Our thanks are due to Dr. G. Scarlett, who referred this case to us, to Dr. Cotton Kennedy and Mr. D. Neill for their help with the laboratory investigation, and to Dr. Colin Brennan for clinical supervision. It is a pleasure also to acknowledge the invaluable secretarial help of Miss Joan Coburn. We wish to thank Organon Laboratories Limited for the supply of compound S.

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EPIDEMIOLOGY OF "SUDDEN, UNEXPECTED, OR RAPID" DEATHS IN CHILDREN

BY

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Fatal disease in children after the perinatal period falls into four fairly distinct groups: (1) unnatural accidents; (2) neoplastic disease; (3) congenital abnormalities of form or function; and (4) rapid, unexpected death occuring either at home or shortly after admission to hospital. Our hospital beds are filled with the children of the first three groups, but the children of group 4 are rarely seen by a paediatrician, and even more rarely by the conventional paediatric research team, and there is a tendency to overlook them or assume that the deaths in this group are outside the responsibility of the hospital.

In Sheffield we are fortunate in that, through the co-operation of the coroner, the general practitioners, and the pathologist in charge of the local regional hospitals, virtually the whole of the natural deaths in children, from a fairly well circumscribed community of over half a million, have tended to pass through a single paediatric pathology department. The variation in the types of death probably reflects as complete a picture of infant mortality as is seen anywhere in the country.

When we first began doing necropsies for the coroner we were struck by the similarity in anatomical findings between the children referred to the coroner as possible cases of home suffocation and the children dying in hospital after a short illness. A careful study of the histories of a series of 50 such "sudden deaths" was carried out in conjunction with the hospital almoner; this confirmed the findings of Bowden and French (1951) that the majority of histories given to the coroner were incomplete. In over 90% there was a history of symptoms beginning at least 48 hours before death (Emery and Crowley, 1956). It thus seemed that it was something of "chance" whether a child died at home or in hospital. For that reason we have now surveyed the deaths of children who, from the histories available, had symptoms for 48 hours or less prior to death, irrespective of the site of death.

Material and Selection of Cases

During the seven years from June, 1949, to May, 1956, we carried out 1,250 necropsies in which the clinical histories were available and adequate for study. Of these deaths, 654 occurred over the age of 7 days. Only these are discussed in the present paper, as the pathological features causing death are likely to be different under this age.

Of the 654 children, 249 had died with a total history of symptoms for 48 hours or less, and from what appeared to be natural acute illnesses. There were a further 10 deaths from unnatural accidents, such as road accidents, and 8 children died as a result of a "cold" operation in hospital.

Variation in Proportion of Deaths During the Seven Years

The total annual number of children examined during the period of study was remarkably stable, being: 1949–50, 88; 1950–1, 92; 1951–2, 98; 1952–3, 100; 1953–4, 90; 1954–5, 99; 1955–6, 87. The proportions

of rapid deaths in these corresponding years were: (excluding road accidents and cold operative deaths) 1949–50, 22 (25%); 1950–1, 37 (40%); 1951–2, 33 (33%); 1952–3, 42 (42%); 1953–4, 46 (51%); 1954–5, 31 (31%); 1955–6, 38 (43%). These figures suggest an increase in the proportion of rapid deaths over the years studied.

It is possible that the general population of children coming to the hospital during this period may have changed, but the only change known to have occurred was an increase in the number of children sent from hospitals in surrounding cities for further investigations. This would increase the number of deaths from diseases of more than 48 hours' duration. The rapid deaths came, of course, from places within a relatively short distance from the hospital. If the numbers of rapid deaths had in actuality remained the same our overall proportions would have shown a diminution. Since our proportions show a tendency to increase, it would seem justifiable to conclude that there was a real increase in the proportion of children dying from acute diseases during this period.

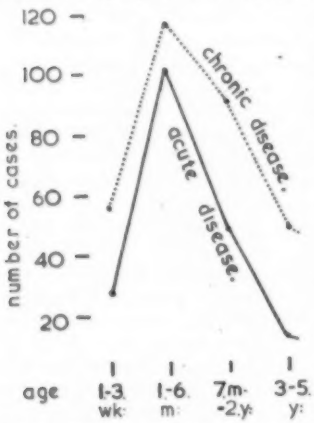

FIG. 1.—Number of children examined dying of disease of under 48 hours' duration, and those of longer duration.

Age at Death

The relative numbers of children dying from disease with symptoms for 48 hours or less compared with the other deaths at the same time in the hospital are expressed in Fig. 1. These two curves show a peak in the age group 1–6 months. The latter part shows a relative increase in deaths from chronic disease. The proportion of very acute diseases was remarkably constant up to the age of 1 year. From the age of 1 year onwards an increasing proportion of deaths occurred from diseases of longer duration.

Time of Year

The total deaths for the different months of the seven years, together with the numbers of children dying from acute disease, are given in Fig. 2. The percentage of acute deaths related to the total number of deaths in the different months is shown. The greatest number of deaths occur during the period December to February, but the proportion of deaths from very acute illness is higher during the later winter months than during the later summer months.

month: J. F. M. A. M. J. J. A. S. O. N. D.
Percentage acute illness in total number of cases
50
40
30
20
Total deaths: 81 59 73 39 58 57 47 42 45 63 43 47
Acute disease: 39 30 23 16 20 14 16 12 15 23 21 20

FIG. 2.—Number of children dying in a five-seven-year period; number dying of acute disease and their relationship at different months of the year (excluding road accidents and cold operations).

Site and Day of Death

Of the 249 deaths from acute disease, 120 occurred at home, 13 in the ambulance on the way to hospital, and 116 after admission to hospital. In view of the observation that cot deaths appear to occur more often at the week-end than the rest of the week, it was thought worth while to relate the site of death to the day of the week. The results of this are shown in Fig. 3.

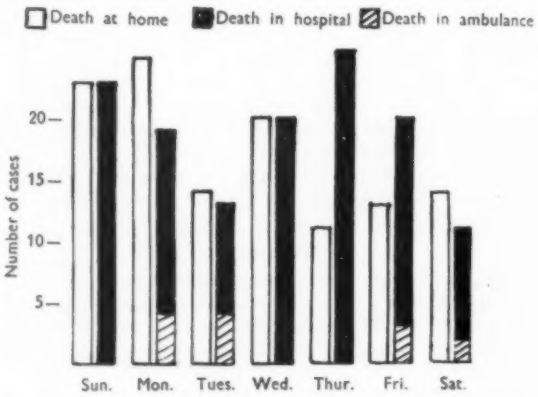

FIG. 3.—Number of deaths from acute illness on different days of week, and site at which deaths occurred.

Since it is sometimes uncertain which side of midnight a child died, we have classified the day of death as including the previous night. A common history is that the child was alive when fed at approximately 11 p.m. and was found dead at 8 a.m., and on that basis we felt it best to assume that death occurred after midnight—that is, deaths occurring during the Sunday night after the child had been put to bed, and in which the child was found dead on the Monday morning are grouped as Monday deaths. There are two points of interest in Fig. 3: first, the relatively slight overall difference in the total number of sudden deaths during different parts of the week; and, second, the difference between the site of death in the latter half of the week and those at the week-end. On Thursday—that is, Wednesday night and Thursday—approximately the same number of children died as on Sunday night and Monday, but the site of death is quite different. There would appear to be a tendency for death to occur at home during the week-end and in hospital during the week.

"Face-down in Pillow"

What appeared to be an accurate description of the position in which the child was found dead was available in 84 children. The position of the child related to its age is expressed in Fig. 4. These figures have only relative value, as we are not able at this point to state the exact proportion of children who would normally sleep in either the face-up or the face-down position. Two things, however, appear: one is

that there seems to be a relatively large proportion of deaths "face down" during the first month, when it is extremely unlikely for a child to be able to turn itself on to its face unless it was virtually placed there originally; and, secondly, the relatively even distribution of face-down position was not found over the age of 9 months. These figures may be biased, as there is a tendency to report the position of a child being found dead face-down and not record the position when the child was face-up. A large number of histories are definite one way or the other, and this point is always recorded when taking histories from coroners' cases. The face-down position does not presumably occur in ambulance deaths, as the children are under constant supervision during this time, but these cases are not included in Fig. 4.

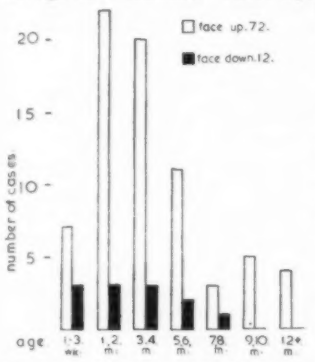

FIG. 4.—Position in which child was found dead related to age of child.

Necropsy Findings

It is not proposed to discuss pathological problems to any extent. Why one child dies with such a minimal amount of, say, pneumonia as to require careful histology to reveal it, and another child survives gross pulmonary infection, is one of the most intriguing problems of pathology. Here are listed only the general pattern of morbid anatomical lesions found. Of the 249 cases, disease of long standing was found in 83; in 37 of these the deformity had been previously known to exist; in 46 the diagnosis was made only after death. The deformities formed a wide range, including many congenital abnormalities of the heart, mongolism, bilateral hydronephrosis with infection, diaphragmatic hernias, etc. Of the remaining cases, lesions which were possibly of pathological significance were found in 145, and in 21 no morbid anatomical diagnosis of any known significance was seen. These 21 children varied in age from 23 days to 5½ months: seven died in bed with parents, two in hospital, nine face-up, three face-down.

Principal Lesions Found in a Survey of 249 Deaths in Children Giving a History of Disease of Less Than 48 Hours' Duration

Disease of long standing			83
Diagnosed during life		37	
Heart disease	12		
Chronic sepsis	0		
Diagnosed after death		46	
Heart disease	8		
Chronic sepsis	10		21
No pathological lesion found			
Acute infection of respiratory tract			112
Acute infection of upper respiratory tract	24		
Laryngotracheobronchitis	35		
Acute suppurative bronchiolitis	13		
Bronchopneumonia	30		
"Necrotizing bronchitis"	10		
Oedema of the lung			57
Meningitis			14
Septicaemia			35
Onset of a known infectious disease			11
Waterhouse–Friderichsen syndrome			19
Pertussis			7
Acute hepatitis			5
Polioencephalitis			5

The general pattern of lesions found does not differ greatly from that seen in other surveys (Bowden and French, 1951), and can best be assessed from the Table and the age distribution of some of the common cases in Fig. 5.

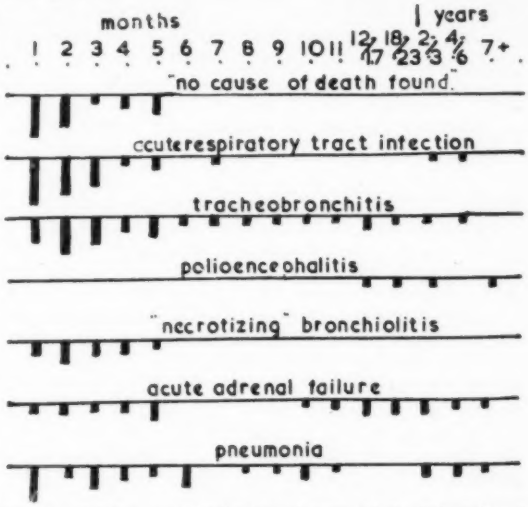

FIG. 5.—Relative age distribution of some of the lesions found in present series of child deaths.

The first most striking feature is the high proportion of child deaths coming into this survey. Here are combined both early hospital deaths and home "cot" deaths. In a series of 150 hospital deaths in 1955, 66 were in children dying within 24 hours of admission (*B.M.J.*, 1957). A difficulty in assessing the relative incidence in the general population is that the certification of these deaths is very variable in some areas. Death from "suffocation" is recorded in some localities; in others "acute pneumonia" will cover the same cases. In a study of accidents in childhood, Boucher (1958) records 415 deaths from suffocation out of a total of 692 children dying at home under the age of 4 years in 1955, and in the years 1950–4 the death rate per million from accidents under the age of 1 year was 749 "suffocation" compared with 28 burns and scalds, and 6 motor accidents. This ratio is reversed in later childhood. Deaths ascribed to accidental suffocation per annum are quoted at 200 (*B.M.J.*, 1958), and 20% of a series of 1,400 deaths in 1955 (Banks, 1958). Swinscow (1951) gives the figures from 1940 to 1949 at between 446 and 911 a year.

In the present series there appears to have been an upward trend in the proportion, varying from 25% to 46%, and one would expect that, in an area which does not contain a hospital liable to attract children likely to die from chronic and rare diseases, the proportion of deaths in this category would approach 50% of all infant deaths. The deaths were not all in children who had been completely normally formed, but congenital abnormalities of themselves likely to cause death accounted for less than 10%. The residue were to all appearances normally formed, and but for this "natural accident" of fulminating illness would presumably have had a normal expectation of life. Over half of the children died either at home or on the way to hospital, and a large number of those who reached hospital died within minutes or a few hours of admission. It is probably an understatement to say that three-quarters of these children died before they were even examined by a paediatrician.

Our figures show, in common with all other surveys, an increased proportion of child deaths in the category under 1 year and a diminishing proportion over this age. Also, from a study of the time of the year and the relative proportions of sudden death, we find that, on top of the known annual variation in the time of these acute deaths (Bowden and French, 1951 ; Stowens, 1957), the proportion of sudden deaths, as well as the absolute numbers, is also much higher in this period.

The apparent variation in site of death during the week and week-end could be a reflection of the patient–doctor relationships at different times of the week—that is, in a number of cases, when I have been able to discuss the child's death later, it seems that the parents knew that the child was ill. They did not realize that it was severely ill, and thought that they would wait until the doctor was back or on duty again on Monday before calling him in, or taking the child to the surgery. It would seem likely that this increased death rate at home at the week-ends is a reflection of this attitude of parents to the medical profession. Parents have also stated that they have known that their own doctor was not on duty at the week-end, and that one of the partners would be called in, and for that reason they had delayed calling in a doctor.

The feature, however, which is probably of even more importance is that an almost similar number of deaths occur during the week-days as at the week-end, which suggests that, even if the doctors had been called to the children, in a large number of instances the death could not certainly have been prevented. On the other hand, we know of many instances in which, but for the prompt intubation and aspiration in the reception rooms of the hospital, children would have died from tracheobronchitis.

Summary

A study was made of 249 children over the age of 7 days who died in Sheffield during the years 1949 to 1956. During these seven years the number of deaths from disease with symptoms of less than 48 hours' duration appeared to remain constant, and possibly increased relative to other diseases.

The proportion of rapid deaths from disease of longer standing appeared to remain constant up to the age of a year. Over that age rapid death became less common.

Death face-down in a pillow showed no particular age distribution.

Of the deaths 120 occurred at home, 13 in an ambulance, and 116 in hospital.

Rapid deaths appeared to be both absolutely and relatively more common in the winter than in the summer months of the year.

While the total number of deaths varied little on different days of the week, there appeared to be a greater tendency for deaths to occur at home at the week-end, and in ambulance or hospital on a week-day.

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DIURETIC EFFECT OF HYDROFLUMETHIAZIDE

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Following the synthesis of chlorothiazide, a benzothiadiazine derivative, various studies, including those of Ford *et al.* (1957) and Bayliss *et al.* (1958), showed that it was the most effective compound yet produced in the search for non-mercurial and non-carbonic-anhydrase-inhibiting oral diuretic agents.

Hydroflumethiazide (6-trifluoromethyl-7-sulphamyl-3, 4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide) is a new benzothiadiazine derivative. This paper reports the response of 21 oedematous patients treated with this drug, and also the effect of a single dose of hydroflumethiazide on the pattern of urinary excretion in five non-oedematous males.

Preliminary studies (Kobinger and Lund, 1958; Holbolth *et al.*, 1958; Sele, 1958) have shown that hydroflumethiazide is an effective oral diuretic and is between 15 and 20 times more active than chlorothiazide in comparable dosage. The present studies confirm this diuretic effect and in addition show that hydroflumethiazide does not significantly inhibit carbonic anhydrase.

Method

Twenty-one consecutive patients with oedema were treated with hydroflumethiazide. The patients were observed for a minimum of three days before hydroflumethiazide was given, except for five cases whose clinical condition did not justify delay. With three exceptions the duration of hospital treatment was between three and four weeks. Half the patients had received various diuretics, and all except three of the cases of heart failure (cases 7, 11, and 12) had been digitalized before admission. Throughout their stay in hospital patients received a low-sodium diet (15 mEq daily). Potassium supplements were not given as a routine. Hydroflumethiazide was given in a dose of 100 or 200 mg. at 6 a.m. and 12 noon on four consecutive days per week. Patients were weighed daily, and 24-hour urine collections were made from midnight to midnight. Weekly blood counts were performed, and serum electrolytes were measured at least once a week. In nine patients urine electrolytes were measured daily.

In the study of the effect of a single dose of hydroflumethiazide the subjects were five adult male convalescent patients who had never been oedematous. On the control day urine was collected under liquid paraffin every two hours for the first 12 hours, and the urine passed in the last 12 hours was collected and studied as a single specimen for each patient. The volume and sodium, potassium, and chloride content of each specimen were measured, and on the specimens

passed during the first 12 hours the *p*H, titratable acidity, and bicarbonate content were also estimated immediately after collection. A similar procedure was followed on a subsequent day after 400 mg. of hydroflumethiazide had been given at 8 a.m. On the control and test days the food and fluid intake of each patient were matched.

Standard chemical methods were used for estimations. Sodium and potassium were measured by flame photometry, chloride by mercuric-nitrate titration (Schales and Schales, 1941). The *p*H of the urine was estimated with the glass electrode *p*H meter. The carbon dioxide was measured manometrically and the urine bicarbonate was derived from the carbonic-acid–bicarbonate curve according to *p*H (Peters and Van Slyke, 1932). The titratable acidity was measured by titration of the urine with standard NaOH to a *p*H of 7.4, measured with the glass electrode.

Results of Clinical Trial

Twenty patients with congestive cardiac failure and one with the nephrotic syndrome were treated with hydroflumethiazide. The cases are summarized and classified according to their aetiology in the accompanying Table. In 16 of the patients with congestive cardiac failure there was a satisfactory response. These patients became free of oedema, and there was no recurrence when they were fully ambulant before discharge. This response did not bear any relation to the underlying cause of the heart failure.

The patient with the nephrotic syndrome (Case 21) had developed oedema while receiving 200 mg. of cortisone daily. She responded well to hydroflumethiazide, and was free of oedema on discharge, having been maintained on the same dose of cortisone throughout her stay in hospital.

During this study four of the patients who had severe heart failure died. The details of these cases are as follows.

Case 4.—A patient with aortic stenosis and incompetence in severe low-output failure who showed no response to hydroflumethiazide.

Case 13.—A patient with hypertensive heart disease and recurrent attacks of congestive cardiac failure. Her initial response to hydroflumethiazide was moderate, and after the addition of 2 ml. of thiomerin on alternate days she showed an improved diuresis. Nevertheless, some oedema persisted until her death.

Case 16.—A patient with cor pulmonale secondary to pulmonary fibrosis. She failed to respond to hydroflumethiazide. Thiomerin, 2 ml. on alternate days, was added, and after the first injection she showed a slight diuresis. Further injections were without effect, and oedema persisted until she died.

Case 19.—A patient with a syphilitic aortic aneurysm which had recently ruptured into the pulmonary artery. After an initial good response he died in irreversible high-output failure.

Analysis of Cases

Diagnosis	Case	Age	Hydroflumethiazide mg. per Day (4 Days per Week)	Loss of Weight lb.	Loss of Weight kg.	Comment
Rheumatic heart disease	1	78	200	13	5·9	Free of oedema on discharge
	2	51	200	18	8·2	,, ,, ,,
	3	53	200	8	3·6	,, ,, ,,
	4	42	200	0	0	Died. See text
	5	60	200	6	2·7	Free of oedema on discharge
	6	58	400	4	1·8	,, ,, ,,
	7	70	400	6	2·7	,, ,, ,,
	8	37	400	11	5·0	,, ,, ,,
	9	43	400	20	9·1	,, ,, ,,
Hypertensive heart disease	10	76	200	7	3·2	Free of oedema on discharge
	11	60	400	3	1·4	,, ,, ,,
	12	57	400	8	3·6	,, ,, ,,
	13	72	400	5	2·3	Died. See text
Cor pulmonale	14	68	400	6	2·7	Also had carcinoma of prostate. Gained 5 lb. (2·3 kg.) on stilboestrol while continuing hydroflumethiazide
	15	53	400	40	18·1	Free of oedema on discharge
	16	56	400	0	0	Died. See text
Ischaemic heart disease	17	59	200	7	3·2	Free of oedema on discharge
Thyrotoxic heart disease	18	72	200	6	2·7	Free of oedema on discharge
Syphilitic aortitis	19	38	400	16	7·3	Died. See text
Congenital heart disease	20	25	200	9	4·0	Free of oedema on discharge
Nephrotic syndrome	21	42	400	12	5·4	Free of oedema on discharge

In the nine patients in whom urinary electrolytes were measured daily, it was found that the maximum sodium and chloride excretion coincided with the maximum water diuresis, which was usually on the second day of the first course. Sodium excretion on the day of maximum response ranged from 60 to 300 mEq in 24 hours, and at first the loss of sodium tended to be slightly greater than the loss of chloride. As the oedema decreased and the sodium excretion fell, the diuretic produced in some cases a disproportionately greater chloride excretion. In none of the 21 cases was any significant change in serum-sodium level noted. Most cases developed some hypochloraemia, with serum-chloride figures of 90 to 95 mEq per litre.

The amount of potassium lost in the urine was extremely variable. In most cases hydroflumethiazide produced some increase in potassium excretion, which was more pronounced when the sodium diuresis had declined.

The average potassium loss on days on which hydroflumethiazide was not given was 33 mEq daily. This compares with the average excretion of 34 mEq of potassium daily during the first course of hydroflumethiazide and with 42 mEq daily during the final course before discharge. The greatest increase in the potassium excretion was seen in Case 17, whose average potassium loss without hydroflumethiazide was 44 mEq daily, and this rose to an average of 70 mEq daily during treatment.

A fall in potassium levels below normal was noted in 16 cases. The greatest differences between the initial and the final serum-potassium level was 1.3 mEq and the average fall was 0.6 mEq.

The only serum-potassium level below 3 mEq per litre was found on one occasion in Case 9, when it was 2.8 mEq per litre; but two days later this had risen to 3.4 mEq per litre. This case, and three others with serum-potassium levels between 3.1 and 3.4 mEq per litre, were the only patients with a serum-potassium below 3.5 mEq per litre after the last course of hydroflumethiazide. All these patients had previously received

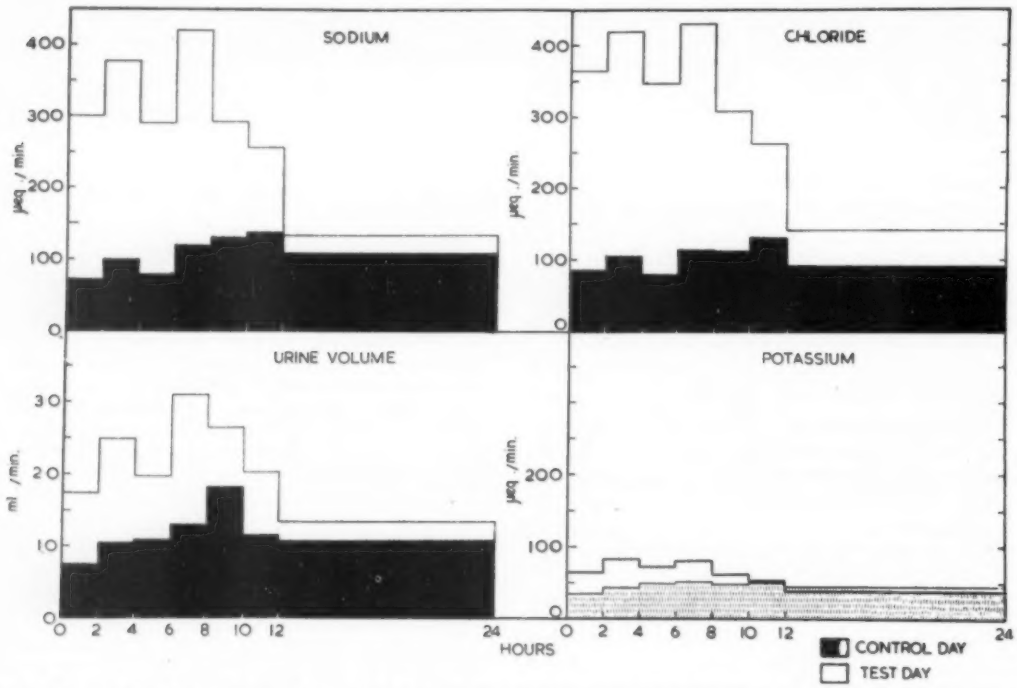

FIG. 1.—Comparison of average urine volume and sodium, potassium, and chloride excretion in five subjects over 24 hours on control day and after administration of 400 mg. of hydroflumethiazide.

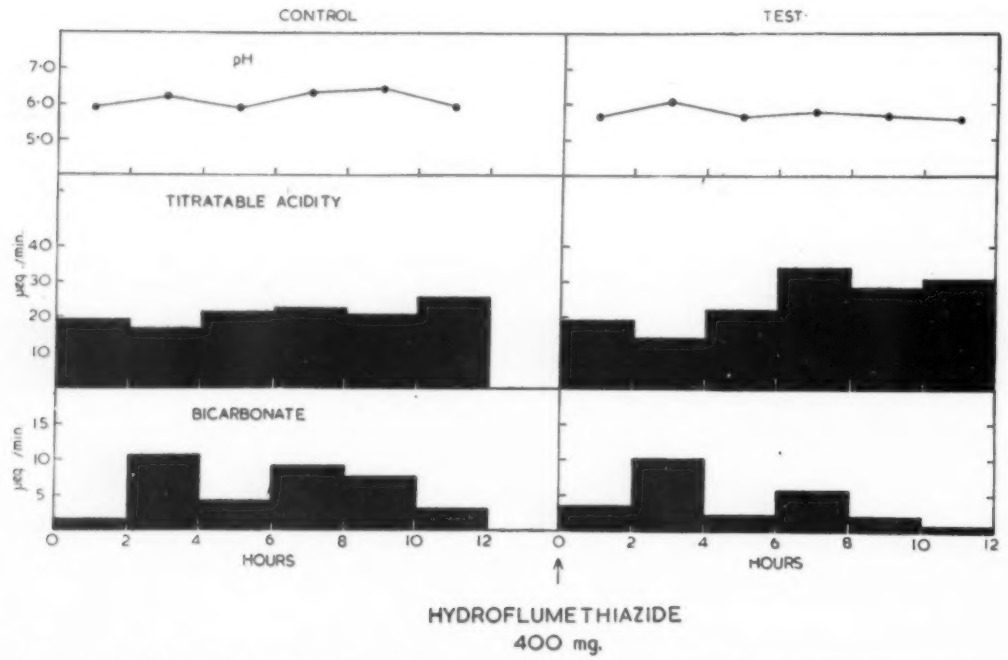

FIG. 2.—Comparison of average *p*H, titratable acidity, and bicarbonate excretion in five subjects over 12 hours on control day and after administration of 400 mg. of hydroflumethiazide.

diuretics and had some degree of hypokalaemia on admission. No symptoms attributable to hypokalaemia were observed.

No side-effects were observed during treatment with hydroflumethiazide, and weekly blood counts showed no significant changes.

Response to Single Dose of Hydroflumethiazide

The effect of 400 mg. of hydroflumethiazide on the urine volume and sodium, potassium and chloride excretion is shown in Fig. 1, which compares the average excretion on the control day and the test day in five subjects. While the maximum effect of the drug is seen during the first eight hours, the urine volume and sodium and chloride excretion continued to be greater throughout the 24 hours of the test day. The potassium excretion, however, was less during the last twelve hours of the test day than on the control day. The excretion of chloride was slightly greater than that of sodium.

The sodium excretion on the test day was 2.1 times greater than on the control day, and at its maximum was 4.1 times greater. The potassium excretion was 1.2 times greater over the control day than over the test day, and was 1.8 times as great at its maximum.

The effect of hydroflumethiazide as a carbonic-anhydrase inhibitor was investigated by measuring the alteration in urinary *p*H titratable acidity, and bicarbonate excretion for twelve hours after the test dose. Fig. 2 illustrates the findings, and shows that there is no increase in the urinary *p*H or bicarbonate excretion, and no fall in the titratable acidity. There is thus no evidence to suggest that hydroflumethiazide significantly inhibits carbonic anhydrase activity.

Discussion

It has been shown in these studies that hydroflumethiazide in doses of 200 or 400 mg. daily is an effective oral diuretic. While no direct comparison has been made, the results suggest that on a weight-for-weight basis hydroflumethiazide is very much more active than chlorothiazide.

Studies of the diuretic effect of chlorothiazide (Ford *et al.*, 1957; Matheson and Morgan, 1958) have shown two modes of action. Like the mercurial diuretics, its primary action is to increase the excretion of chloride. In addition it resembles acetazolamide in inhibiting carbonic anhydrase and thus increasing bicarbonate excretion. It has been suggested (Slater and Nabarro, 1958; Matheson and Morgan, 1958) that the inhibition of carbonic anhydrase may be partly responsible for the hypokalaemia which sometimes complicates treatment with chlorothiazide.

Hydroflumethiazide resembles chlorothiazide and the mercurial diuretics in that it produces an almost equimolar loss of sodium and chloride. Unlike chlorothiazide or acetazolamide, however, it produces no increase in the *p*H of the urine or in bicarbonate excretion and no fall in hydrogen-ion excretion estimated from the titratable acidity. It therefore appears that hydroflumethiazide does not significantly inhibit carbonic anhydrase, although, like chlorothiazide, it contains the free SO_2NH_2 group in its molecule, to which this action is attributed (Mann and Keilin, 1940). These findings are confirmed by the laboratory observation that it is 100 times less active than chlorothiazide and over 5,000 times less active than acetazolamide in this respect (W. F. J. Cuthbertson, personal communication, 1959).

Our results show that hydroflumethiazide produces some increase in potassium output in association with the greatly increased excretion of chloride. However, as hydroflumethiazide does not significantly inhibit carbonic anhydrase the additional loss of potassium through this action should not occur. This may help to reduce the likelihood of potassium depletion and the necessity for potassium supplements during treatment with drugs of the benzothiadiazine group.

Summary

A trial of a new non-mercurial oral diuretic, hydroflumethiazide, is reported. Seventeen out of twenty-one oedematous patients responded well to doses of 200 or 400 mg. daily. Two patients showed no response, and in two others an initial response was not maintained: these four patients ultimately died.

No toxic effects attributable to hydroflumethiazide were seen in any patients.

A study of the response to a single dose showed a marked increase in sodium and chloride excretion with no increase in bicarbonate loss. It therefore appears that hydroflumethiazide does not significantly inhibit carbonic anhydrase.

While some increased potassium excretion has been demonstrated, absence of significant carbonic-anhydrase inhibition might be expected to reduce the degree of potassium depletion.

We wish to thank Dr. Oscar Brenner for his interest and for allowing us to study patients under his care; Dr. J. N. Marshall Chalmers and Mr. Garfield Thomas for facilities and advice; Miss I. Florence for some of the urine electrolyte estimations; and Glaxo Laboratories, Ltd., for supplying the hydroflumethiazide ("NaClex").

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A new 204-bed hospital, designed to be "noiseless and odourless," was opened earlier this year in California as an addition to the Fresno Community Hospital. The 500-ton air-conditioning plant installed in the new buildings permits a difference in air pressure in corridors, rooms, and bathrooms, thus preventing the escape of odours from one to the other. To reduce noise, nylon carpets have been fitted in the halls and corridors, and acoustical ceilings and special vinyl-plastic-covered walls in the public areas. Other features are an all-electric kitchen from which food is served to patients in seven minutes, a pneumatic tube system for messages and small packages, and a central dictating system which enables doctors to dictate their notes by telephone from any part of the hospital. (*News Bulletin*, August, 1959, International Hospital Federation.)

HYPOTHERMIA AFTER CHLORPROMAZINE IN MYXOEDEMATOUS PSYCHOSIS

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We report here the case of a patient who developed myxoedematous psychosis and then lapsed into hypothermic coma after an injection of chlorpromazine.

Case Report

The patient, a housewife aged 54, was born in Italy, and came to England at the age of 21. In 1943 she developed thyrotoxicosis and was found to have a nodular goitre, so a partial thyroidectomy was done. She was well thereafter until a year ago, when she began to complain of feeling cold. Two weeks before admission she told her family that the neighbours had turned against her, and that people she met in the street would not look at her or speak to her. Three days before admission she took to her bed, saying that she had split into two pieces, and was living in the left half only. Next day her mental state was worse, and on the day before admission she said that she was now the Queen of Heaven, and that her subjects were telling her to scratch herself. When her family doctor saw her she screamed at him and told him that he was a thief. She was admitted to a mental hospital that night.

When examined there she was found to be maniacal and violent, and was screaming persistently. She was given 100 mg. of chlorpromazine by intramuscular injection; next morning she was quiet but was unable to answer questions, and kept mumbling that she was cold. Methedrine was given (30 mg. intramuscularly) and she became a little more alert, but later in the day she could not be roused. As she was thought to have had a cerebral vascular accident one of us (R. G. W.) was asked to see her, and she was then transferred to the Radcliffe Infirmary.

On examination she was fat and pale, with a cold dry skin. The rectal temperature was 92° F. (33.2° C.). Her hair was coarse and sparse, but the body hair was normal. No peripheral pulses could be felt and the blood pressure was unrecordable, but heart sounds could be heard, the rate being 40/minute.

She would respond to questions by making a croaking, unintelligible noise. The pupils were widely dilated and did not react to light. The limbs were flaccid, the tendon reflexes were just present, and there was a very slow relaxation phase. The plantar responses were extensor.

Initial Investigations.—Blood sugar, 118 mg./100 ml. Serum cholesterol, 400 mg./100 ml. Electrolytes (mEq/l.), Cl, 100; HCO_3, 17; Na, 130; K, 3.5. Chest and skull *x*-rays normal. Blood urea, 65 mg./100 ml. E.C.G.—sinus bradycardia; low-voltage complexes and flat T waves. E.E.G.—sleep pattern. Blood count: Hb, 80%; W.B.C., 10,000/c.mm. W.R. negative.

Management

She was given 40 μg. of triiodothyronine intravenously, and was then immersed up to the neck in a bath of water at 98° F. (36.7° C.). Four hours later her rectal temperature was 100° F. (37.8° C), so she was taken out of the bath and put into a warmed bed. Half an hour later her temperature was 98° F. (36.7° C.), and although she was confused she was able to answer questions and take food and fluid by mouth. Tendon reflexes were brisk, pulse rate 90/min., blood pressure 85/60, and pupils reacted briskly to light. A second intravenous injection of 40 μg. triiodothyronine was given.

The blood pressure steadily rose, and 12 hours from the start of treatment she was alert and cheerful, although still slightly confused. The plantar responses were now flexor, the serum cholesterol was 200 mg./100 ml., and there was no change in blood-sugar or electrolyte levels. She was given triiodothyronine, 20 μg. orally, three times a day, thereafter, but after 48 hours her mental state had deteriorated; she was very confused and apathetic, and could not take fluids by mouth. The blood-pressure fell from 130/90 to 85/60, and the plantar responses became extensor. An E.E.G. at this time showed frequent stretches of sleep pattern. Hydrocortisone 40 mg. was given intravenously; 24 hours later the blood-pressure was 140/90, the plantar responses were flexor, and she was able to eat, drink, and answer questions. Forty-eight hours later, however, the blood pressure had again fallen to 90/60 and she had reverted to her former mental state. A further 40 mg. of hydrocortisone was given intravenously, and in 24 hours the blood-pressure rose to 140/90. She became alert, cheerful, and rational, and remained perfectly well, with no abnormal physical findings thereafter.

Throughout this period the blood sugar had been normal, but the blood urea had risen to 83 mg./100 ml. In the second week of her admission her plasma chloride level had fallen to 83 mEq/l., and the serum sodium was 127 mEq/l., the blood urea being 90 mg./100 ml. She was given sodium chloride supplements (6 g. a day by mouth); a week later the plasma chloride level was 103 mEq/l., and the blood urea was 40 mg./100 ml. There was, it seemed, some element of adrenal insufficiency, so in the fourth week of her admission the following tests were done:

1. *Modified Thorn Test.*—25 units of corticotrophin was infused intravenously over an 8-hour period. On the day of the test the blood urea was 34 mg./100 ml., and the electrolyte levels (mEq/l.) were Cl 108, Na 133, K 4.4, HCO_3 27. The result of the test is set out in the accompanying Table, and shows that the adrenals were capable of responding normally to stimulation with corticotrophin.

Effect of Infusing 25 Units of Corticotrophin Intravenously

Day	Eosinophils/c.mm.		24-Hour Urinary Excretion		
	10 a.m.	4 p.m.	17-Ketosteroids (mg.)	Na (mEq)	K (mEq)
1	30	47	1·8	110	30
2*	34	6	4·0	70	35
3	15	25	1·4	260	27

* Corticotrophin 25 u. i.v. 10 a.m.–6 p.m.

2. *Water-Load Test.*—After 1,200 ml. of water by mouth, 81% was excreted in the next four hours, the maximum urine flow being 8 ml./min.

During her convalescence thyroid extract, ½ gr. (33 mg.) three times daily, was gradually substituted for the oral triiodothyronine; at the end of the fourth week she was alert, cheerful, and completely rational, although she felt that the other ward patients were talking about her and were unfriendly. At this stage the sodium chloride supplements were stopped and she was sent home. She was completely unable to recall the happenings in the two weeks before and the week after her admission to hospital.

She has been seen regularly during the six months since she left hospital, and on thyroid ½ gr. (33 mg.) three times a day is normal, mentally and physically. The blood urea, cholesterol, sugar, and electrolyte levels are normal.

Discussion

Two important points arise from this case. Firstly, the relationship of the hypothermic coma to the injection of chlorpromazine; secondly, the fact that the patient survived.

Delay and Deniker (1952) showed that chlorpromazine caused a marked fall in basal metabolic rate, and this was confirmed by Ratschow (1953). Marocco and Brena (1953), working on guinea-pigs, showed that chlorpromazine reduced the uptake of ^{131}I by the thyroid gland; Milcou *et al.* (1957) found that, in the rat, chlorpromazine lowered the basal metabolic rate and produced large colloid-filled thyroid follicles. It seems, therefore, that chlorpromazine depresses thyroid activity, and this may account for the development of hypothermic coma in our patient after an injection of 100 mg. of the drug. As a similar dose given intravenously does not produce hypothermia in clothed patients (Shackman *et al.*, 1954) it is unlikely to be a direct effect of the drug.

Recovery from hypothermic myxoedema coma is unusual. Of the 19 patients reviewed by Macdonald (1958) only three survived, and one of these died a month later. It is hardly surprising, therefore, that there has been considerable discussion on the management of these moribund patients. Our patient, and two out of the other three who recovered from the hypothermic coma, received triiodothyronine intravenously. There is no doubt that it has the most rapid action of any of the available thyroid hormones (Asper *et al.*, 1953), being effective within a few hours. We used relatively small doses (two injections of 40 μg., each equivalent to 2 gr. (130 mg.) of thyroid extract), whereas the patient described by Dyson and Wood (1956) was given 1,200 μg. and did not survive.

Forty-eight hours after the hypothermia had been corrected, our patient's blood-pressure fell, but it returned to normal levels after two injections of hydrocortisone. During the second week the blood-urea level rose and the levels of serum sodium and chloride fell. This tendency was corrected by salt supplements, but by the fourth week the extra sodium chloride was stopped, and there has been no tendency to relapse. There thus seems to be clear evidence of a transient phase of adrenal insufficiency. Myxoedematous patients have been shown to have impaired adrenal function (Statland and Lerman, 1950; Beierwaltes and Bishop, 1954; Hubble, 1955), and it has been suggested that the pituitary may also be involved (Statland and Lerman, 1950). If these patients do have both secondary adrenal and pituitary insufficiency, giving thyroid hormones might precipitate adrenal failure, for Lerman and Stebbins (1942) showed that thyroid medication could provoke an Addisonian crisis in patients with hypopituitarism. It seems likely, therefore, that hydrocortisone has a valuable part to play in the treatment of severely myxoedematous patients.

As our patient responded normally to a water load and to intravenous corticotrophin four weeks after starting thyroid replacement therapy, the depression of other endocrine functions by the myxoedematous process is clearly reversible. Crispell *et al.* (1954) and Paull and Phillips (1954) found that thyroid extract and thyroxine corrected the delayed water diuresis of myxoedematous patients, but only after many months of treatment. As our patient responded normally to a water load after four weeks this is probably another indication of the speed with which triiodothyronine acts compared with thyroid extract and thyroxine.

Summary

Fifteen years after thyroidectomy, a woman of 54 developed myxoedematous psychosis. Chlorpromazine (100 mg. intramuscularly) was given and the patient lapsed into hypothermic coma.

External warmth and intravenous triiodothyronine produced rapid improvement; secondary adrenal insufficiency occurred, and was corrected by intravenous hydrocortisone and sodium chloride supplements orally.

We are grateful to Sir George Pickering for permission to report this case. The triiodothyronine used was supplied by Glaxo Laboratories Ltd.

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Medical Memoranda

Problem of Cooling a Gangrenous Leg

Whether to cool or not to cool a gangrenous leg will be the question confronting the surgeon when called upon to treat such a condition. The routine of exposing and keeping cool a gangrenous limb would seem to have been actually harmful in the following case. The thrombosis appears to have been due to the presence of autohaemagglutinins and perhaps to an added local factor. No vascular disease was present.

Case Report

A married woman aged 59 was admitted to hospital in August, 1957, with a discoloration of the toes of the left foot which had occurred three weeks previously. There was no history of vascular disease, injury, or exposure to cold. Tobacco consumption was 5–15 cigarettes a day. Right radical mastectomy had been performed eight years previously with apparently excellent result. There was no diabetes or familial disease. The patient was of non-Jewish extraction, though married to a Jew, who had died several years ago; there were no children.

General examination revealed no abnormality apart from the blue, cold, gangrenous toes of the left foot. Peripheral

pulses were present, and these were stated to have been observed by her general practitioner at the onset. B.P. 120/75 mm. Hg: temperature normal; chest radiography normal. Urine contained a trace of albumin on ward test. Blood-sugar-tolerance curve: fasting, 85 mg./100 ml.; 30 minutes after 50 g. of dextrose by mouth, 119 mg.; 60 minutes, 132 mg.; 90 minutes, 138 mg.; 120 minutes, 138 mg.

The affected limb was exposed to keep it cool, and thus to lower the rate of tissue metabolism and the demand for blood. However, exposure to room temperature caused pain in the leg. To overcome this, average doses of analgesics were administered. Two weeks after admission the peripheral pulses disappeared in the left foot, so a left lower lumbar sympathectomy—removal of the left third and fourth lumbar ganglia—was carried out on September 17. The general condition of the patient was excellent, but the gangrene spread, and in a few days the sole of the foot became cold and blue. A below-knee amputation was carried out a week after the lumbar sympathectomy (September 24).

Routine pre-operative blood grouping first indicated the presence of high titre of cold agglutinins as the cause of the difficulty in the cross-matching. The haemoglobin level at this time was not known, but clinically the patient had a very good colour. To avoid any damage to the vascular system a tourniquet was not used. Blood transfusion was not given, as there was practically no blood loss at the operation. However, she soon became clinically anaemic and the gangrene spread above the amputation stump. Three days later her haemoglobin was only 44%. Blood transfusion caused immediate rigor and collapse, as did several further transfusions in the next few days; meanwhile her haemoglobin dropped to 40%; red blood cells 2,100,000; C.I., 0.95; white cells, 24,000 (polymorphs 84%, lymphocytes 14%, monocytes 2%). Serum bilirubin, 2.5 mg./100 ml. indirect. Urine: bile-positive.

The North London Blood Transfusion Centre suggested giving washed red cells, warmed to body temperature while the patient was kept warm at 100° F. (37.8° C.) by heat cradle, and also advised the administration of antihistamine before transfusion. This procedure was followed, but the first attempt failed, and only after 100 mg. of promethazine hydrochloride and 50 mg. of chlorpromazine hydrochloride intravenously had rendered the patient unconscious was the transfusion successful. By this time her haemoglobin was below 30%. One pint (568 ml.) of packed and washed R.B.C. on three consecutive days raised the haemoglobin to 62% with improvement of the general condition, though the gangrene had spread to the mid-thigh and serum bilirubin increased to 6.5 mg./100 ml. At this time Professor Dacie examined the patient and recorded the following: red-cell fragility, 0.30–0.45% NaCl; cold agglutinins, 1:512 at 2° C. and nil at 37° C.; reticulocytes, 22.8% marked polychromasia, anisocytosis, and microcytosis of the red cells. Blood culture was sterile, and this, with repeated wound swabs, excluded *Clostridium welchii* infection, a possible cause for thrombosis and haemolysis. Paper chromatography for serum proteins—somewhat later—showed normal pattern; no cryoglobulins were present.

Large sacral pressure sores aggravated the situation, but the left leg had to be removed, and therefore, after further transfusions, the left hip was disarticulated (October 15, 1957). At the operation good pulsation was felt in the femoral and external iliac arteries, and there was satisfactory bleeding from the minor vessels before applying the ligatures. The general condition of the patient was satisfactory, and the haemoglobin remained at 60–65% without further transfusions for two weeks. But on November 2 the Hb was 48%, the pressure sores were spreading, and the amputation stump was sloughing. Further transfusions were given, but the toes of the right foot had become blue and cold, and she became drowsy and later comatose. The temperature rose, and the patient died on November 14.

Post-mortem examination by Dr. A. Thomson revealed thrombosis of the left common and external iliac arteries and veins, the arterial thrombus extending into the abdominal aorta, leaving only a little passage for the blood to the right common iliac artery. There was no thrombosis in the latter or in its branches. The heart and coronary vessels were normal, and there were no atheromatous plaques. The spleen was enlarged to twice the normal size. Histology showed thrombosis in both the arteries and veins—common iliac and external iliac—but no vascular disease was present. The amputated leg was also examined by Dr. Thomson soon after it was removed, and the report was identical with the above.

Comment

There are at least three possibilities to explain the pathology in this case. (1) Thrombosis in the left external iliac artery; but pulsation in the vessels has been seen at various amputations, months after the onset of symptoms. (2) Gangrene of the left toes caused the emergence of cold agglutinins, and the latter set up a vicious circle by causing further thrombosis. This explanation still needs a primary cause for the gangrene of the toes. (3) The thrombosis of the digital vessels and gangrene could have been caused by clumping of the red blood cells under the effect of cold agglutinins when the temperature of the toes has been suitably low. The difficulty with this explanation is why only one leg was affected?

Cold agglutinins are known to cause thrombosis (Stats and Bullowa, 1943; Bateman, 1949). Butler and Palmer (1955) added cryoglobulinaemia to the list. Several authors attributed Raynaud's syndrome to cold agglutinins, and it is interesting that the syndrome disappeared when the agglutinins did so (Forbes, 1947; Ch'en Hsi-Mou, 1955).

However, vascular symptoms only rarely occur when cold agglutinins are present (Young, 1946), therefore an additional local factor has to be assumed, such as difference in the vascular meshwork or tissue metabolism. In the case of Forbes (1947), Chen and Chen (1951), and Ch'en Hsi-Mou, (1955) cooling of the hand activated the cold agglutinins. Our patient also complained of pain in the leg when exposed to room temperatures. The haemolysis and jaundice fit into the picture, because either the agglutinated red cells suffered haemolysis or the cold agglutinins caused a haemolytic anaemia. In this mechanism the normal histological structure of the blood vessels is further corroborative evidence.

Acknowledgments are due to Dr. D. K. Mulvany, surgeon in charge of the case, for his permission to publish and for his continuous interest and encouragement; to Professor J. V. Dacie, of the British Postgraduate School at Hammersmith, for kindly seeing the patient; to Dr. A. Thomson for the histological and post-mortem examinations; and to Dr. G. Plaut and the North London Blood Transfusion Service for their zealous co-operation.

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Reviews

JOHN HUGHLINGS JACKSON

Selected Writings of John Hughlings Jackson. 2 Volumes. Edited by James Taylor, M.D., F.R.C.P., with the advice and assistance of Gordon Holmes, M.D., F.R.C.P., and F. M. R. Walshe, M.D., F.R.C.P. (Pp. 500+xiv, 510+viii; illustrated. £6 6s.) London: Staples Press. 1958.

The *Selected Writings of John Hughlings Jackson*, first edited by the late Dr. James Taylor and published in 1930, have long been out of print, and their reprinting has often been discussed. This has finally been achieved by an American publishing company, with the consent of the Guarantors of *Brain*, who sponsored the original edition. The reprint in two volumes is admirably produced.

It is probable that this enterprise owes its main stimulus to the increasing interest being taken in Jackson's teachings in the United States, though this is not to suggest that there will be no demand for the reprint in this country.

Jackson has always had a small but devoted following among neurologists, especially in English-speaking countries, for his prose presents formidable difficulties to those whose mother tongue is not English. Yet it is probably fair to say that he has been "caviare to the general," and that many young neurologists to-day, burdened with the increasing scope of their discipline, find it easy to write him off as a period piece of no clear relevance to the problems now facing them, and far too concerned with general principles to make easy reading. His language, too, is not that of modern neurology or neurophysiology, and the correlation of his thought with modern concepts cannot be easy. Yet despite this there is a growing interest in Jackson in the United States, where Dr. W. Riese has written so much and so understandingly about his teachings and their import.

The story of Jackson's influence upon our thought about the physiology of the cerebral cortex is a strange one, perhaps unique. Ferrier and Hitzig both proclaimed him their precursor in the study of functional localization in the cortex, yet his influence upon current neurophysiological thought was negligible, and at no time since he first wrote have his teachings ever been given an adequate presentation in any textbook of physiology. Even Ferrier in his work, *The Functions of the Brain*, published in the 1880's, does not tell us anything of Jackson's special views on localization, and Jackson himself, writing at this time, declares that he had never seen the views he held about localization mentioned anywhere.

It is probable that this neglect of Jackson arose from his early rejection of "strict localization" on a mosaic plan in the "motor cortex," for the sufficient reason that his own findings of the results of destroying and discharging cortical lesions were incompatible with this view. If Jackson found a mention at all in any nineteenth-century physiological text it was solely in respect of his views on aphasia. Modern texts treat him no more adequately. Jackson has therefore remained a living force only among some of his clinical contemporaries and successors. Nevertheless, recent observations in the field of experimental physiology of the cortex, as, for example, some work of Liddell and Phillips in this country and of Gellhorn in the States, have given a new lease of life to his ideas and have revealed these to be in some respects still in advance of current opinion.

To grapple with Jackson's writings is a difficult task, both from the nature of his ideas and from his literary style and his proneness to parenthesis and to repetition, and they will probably always defeat any reader who has not a vivid interest in the general principles of neurology, and is not prepared to lift his eyes from time to time from the mass of detail of his task in the complex field of the nervous system and its functions. Yet for those who will persevere, the reward can be rich.

F. M. R. WALSHE.

PROBLEMS OF FERTILITY

Studies on Fertility. Including papers read at the Conference of the Society for the Study of Fertility, London, 1958. Volume X of the *Proceedings* of the Society. Edited by R. G. Harrison, M.A., D.M. (Pp. 176+x; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1958.

This makes Volume X of the *Proceedings of the Society for the Study of Fertility*, and 15 of its chapters comprise papers presented by different contributors at the annual conference of the society held in London in 1958. These deal with certain aspects of both male and female fertility, and their subject-matter includes experimental animal studies on the production and transport of spermatozoa and ova, the effect of varicocele on spermatogenesis, the relation of uterine retroversion to female fertility, and psychiatric aspects of infertility. All are well set out with adequate illustrations, and generally display a pleasing critical scientific approach which has not always been observed by workers in the field of human reproduction.

There is much of value in this volume for all those interested in fertility problems, but perhaps the most fascinating and topical contribution is Chapter I, which is entitled "Fertility Control with Oral Medication." This represents the second Oliver Bird Lecture, delivered by Dr. Gregory Pincus, who played a large part in what has come to be known as the Puerto Rico experiment. After describing the background to the use of the 19-nor-steroids to suppress ovulation, and the tests carried out on animals and on human volunteers, he gives the results of the trial conducted in Puerto Rico. Those women who conscientiously took the tablets of norethynodrel (with the 3-methyl ester of ethinyl-oestradiol added) had their fertility temporarily reduced to a significant degree, and that mostly without undesirable side-effects. The full details of the findings are here presented in a concise and easily assimilated way. This chapter alone should attract a large number of readers to the book.

T. N. A. JEFFCOATE.

JOHNS HOPKINS MEDICAL SCHOOL

The Johns Hopkins Hospital and the Johns Hopkins University School of Medicine. A Chronicle. Volume II, 1893–1905. By Alan M. Chesney, M.D. (Pp. 499+xiv; illustrated. 48s.) Baltimore: Johns Hopkins Press. London: Oxford University Press. 1959.

The Dean Emeritus of the Medical Faculty of the Johns Hopkins University has followed up his account of the early years of the Hospital and School of Medicine with a second volume dealing with the founding of the Medical School, and ending in 1905 with Osler's resignation and departure to be Regius Professor of Medicine at Oxford. With the founding of the medical side of the University a new era began in American medical education. The greatness of Johns Hopkins was due to four men—Welch, the pathologist; Osler, the

physician; Halsted, the surgeon; and Kelly, the gynaecologist. Famous already in their profession, they came to the birth of this new school, gave of their best to it, and carried it to the front rank. As a student of those days wrote: "These men were more than doctors; they were teachers and executives, they were lecturers and advisers, they were even actors and propagandists. They had spirit, they had humility, they had knowledge and deep understanding of illness, of disease, and of people—but especially of people." And Dr. Bertram Bernheim wrote*: "Never again will we be presented with such a galaxy of stars at one and the same time." Many of their pupils were distinguished and carried on the tradition either at Johns Hopkins or in other medical schools—for instance, Harvey Cushing, W. S. Thayer, L. F. Barker, W. Longcope, J. Whitridge Williams, and W. W. Francis.

Again and again in this book does Dr. Chesney show how Welch above all was the medical genius of the Medical School, obtained funds for its expansion, and gave it devoted service up to 84 years of age. Our chief criticism of this chronicle is that it pays too much attention to detail, to the inevitable teething troubles which arise with any new departure, and to accounts of incidents and individuals which appeal only to the memories of early students. Also, as the author acknowledges in his preface, it omits the many contributions to science which emanated from the school; nor does it give full justice to the work and events which made Johns Hopkins famous. We hope that in a third volume Dr. Chesney will carry the record farther.

ARTHUR S. MACNALTY.

NEVER SAY DIE

Never Say Die. A Return to Everyday Living for the Partially Disabled. By Anthony Richardson. (Pp. 107. 12s. 6d.) London: Max Parrish. 1959.

Laid low by a stroke which left him partly paralysed in the left arm and leg, the author went through the usual routine of hospital, convalescent home, and physiotherapy. But when all that was over and he was sent home to resume his normal life, which had been a solitary bachelor existence, he was filled with a high determination to master his disability and to regain his social independence. This book is a good-humoured account of his successful campaign. The secret of his success lay in his ability, not only to plan every move in advance, but to rehearse it in detail in his imagination before taking the first step, assessing his environment (which hitherto he had taken for granted as being pretty neutral) in terms of friendly reliable objects and treacherous enemies. With very little power in his left hand he learned to shave, wash, "strip-bathe," and dress himself; and he describes minutely his own personal techniques, even to tying shoelaces and neckties. (Is it generally known, for instance, that one particular brand of safety-razor blade does not have to be removed from its holder and wiped dry?) Within twelve months of his stroke he had not only become completely self-reliant, but had written two books, one play, and 20,000 words of autobiography. A triumph of spirit over weakness of flesh.

This book is destined to grace the Red Cross library trolley in every ward in every hospital. No patient, from whatever disability he may be suffering, could fail to be spurred on towards a fuller life.

GEORGE DAY.

*B. M. Bernheim (1949): *The Story of the Johns Hopkins*, p. 238 The World's Work (1913) Ltd., Kingswood, Surrey.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Proceedings of the Fourth International Congress of Biochemistry, Vienna, 1-6 September 1958. General editor O. Hoffmann-Ostenhof. Vol. III. ***Biochemistry of the Central Nervous System.*** Edited by F. Brücke. (Pp. 324+xi; illustrated. 88s.) London, New York, Paris, Los Angeles: Pergamon Press. 1959.

Atlas of Roentgenographic Measurement. By Lee B. Lusted, M.D., and Theodore E. Keats, M.D. (Pp. 176; illustrated. 68s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers, Ltd. 1959.

Practical Food Inspection. By C. R. A. Martin, M.B., B.S.(Lond.), D.P.H., L.R.C.P., M.R.C.S., F.R.S.H., LL.B. Fifth edition. (Pp. 656+vii; illustrated. £3 3s.) London: H. K. Lewis and Co. Ltd. 1959.

Die Wirbelsäulenleiden und Ihre Differentialdiagnose. Second edition. By Professor Dr. J. E. W. Brocher. (Pp. 457+xv; illustrated. DM. 128.) Stuttgart: Georg Thieme Verlag. 1959.

Chirurgisches Nahtmaterial. Eigenschaften, Sterilität und deren Prüfung. By Harald Hudemann. (Pp. 144; illustrated. DM. 13.50.) Jena: VEB Gustav Fischer Verlag. 1959.

Miscellaneous Notes. By F. Parkes Weber, M.D., F.R.C.P., F.S.A. Third series. (Pp. 8. 2s. 6d.) London: H. K. Lewis and Co. Ltd. 1959.

The Place of Work in the Treatment of Mental Disorder. Proceedings of a Conference held at Church House, Westminster, London, on March 19 and 20, 1959. (Pp. 99. No price.) London: National Association for Mental Health. 1959.

Medizinische Grundlagenforschung. Volume II. Edited by K. Fr. Bauer with 27 contributors. (Pp. 827+viii; illustrated. DM. 168.) Stuttgart: Georg Thieme Verlag. 1959.

Sechzig Jahre Medizinische Radiologie. Probleme und Empirie. By Hans R. Schinz. (Pp. 275; illustrated. DM. 19.50.) Stuttgart: George Thieme Verlag. 1959.

Milk and Milk Products in Human Nutrition. By S. K. Kon. (Pp. 75+ix. 3s. 9d.) F.A.O. Nutritional Studies No. 17. London: H.M. Stationery Office. 1959.

Case Histories in Hypnotherapy. By Arnold Furst and Lester T. Kashiwa, M.D. (Pp. 163. No price.) Los Angeles: Genli Publishing Company. 1959.

L'Hypnose. Problèmes Théoriques et Pratiques. By L. Chertok. (Pp. 78. No price.) Paris: Masson et Cie. 1959.

1958 Highlights of Progress in Research on Cancer. Prepared by the National Cancer Institute. (Pp. 46+v. 25c.) Washington, D.C.: U.S. Department of Health, Education, and Welfare. 1959.

Preventive Aspects in the Teaching of Pathology. Seventh Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. (Pp. 30. 1s. 9d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Role of Hospitals in Ambulatory and Domiciliary Medical Care. Second Report of the Expert Committee on Organization of Medical Care. (Pp. 32. 1s. 9d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Iron Deficiency Anaemia. Report of a Study Group. (Pp. 15. 1s. 9d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Office Orthopedics. By Lewis Cozen, M.D., F.A.C.S. Third edition. (Pp. 430; illustrated. 70s.) London: Henry Kimpton. 1959.

The Artificial Feeding of Normal Infants. By William Emdin, M.D., D.P.H., Ph.D., B.A. (Pp. 113; illustrated. 16s.) Cape Town: Howard Timmins. 1959.

Kurzer Atlas für das Klinische Laboratorium. By Eberhard Goetze. (Pp. 40. DM. 12.75) Jena: VEB Gustav Fischer Verlag. 1959.

Sygehusundersögelsen i Danmark. En Statistisk Analyse af Belaegningsfo holdene på Medicinsk-Kirurgiske Sygehuse 1952-53 and 1930. (Pp. 198. Dan.kr. 34.) Copenhagen: Munksgaard. 1958.

A Primer of Water, Electrolyte and Acid-Base Syndromes. By Emanuel Goldberger, M.D., F.A.C.P. (Pp. 322; illustrated. 45s.) London: Henry Kimpton. 1959.

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BEHAVIOUR OF THE MARKET PLACE

Our new President, Prince Philip, reminded us last week[1] that ethics "is really the crux of any professional organization. . . ." If we are to be honest with ourselves, we must admit that the profession has got into a real tangle over this question. At the Edinburgh meeting of the B.M.A. in July hints were thrown out that the profession's views on ethics needed brushing up, and, hard upon the heels of this, doctors received a rather stern reminder from the Council of the B.M.A. that they should be more circumspect. In this country we distinguish less carefully than some other countries do between ethics and professional etiquette. Maybe there is some virtue in British ambiguity in this matter because the two so often overlap. There is, however, obviously a world of difference between rules which prescribe what a doctor may display on his brass plate and an ethical code which condemns fee-splitting and the seduction of a patient as infamous professional conduct. In between these extremes there is a variety of behaviour which is regarded as unprofessional and centres round the fact that doctors should not, through deliberate publicity, encourage the public to believe that they are better doctors than their fellow practitioners. Comparisons, as Mrs. Malaprop meant to say, are odious.

All professions are opposed to any one of their members seeking to gain an unfair advantage over others in attracting clients or patients. Hitherto the medical profession has had the reputation of being more strict in this respect than other callings. This is as it should be, because by the nature of his work the practising doctor comes into a more intimate relationship with the people he cares for than does any other professional man. Apart from the purely material gains to the publicist from attracting patients by unethical means, there is a grave risk that the confidence of patients in their own doctors may be diminished as the result of publicity which focuses attention upon the alleged professional excellence of the person publicized.

[1] *Brit. med. J.*, 1959, 2, 839.

It is astonishing to notice that according to some protagonists ethical rules should be relaxed in this age of broadcasting and television. This is equivalent to saying that as gin has a greater alcoholic content than beer people ought to drink more gin. Television provides a medium for publicity so much more powerful than anything else that the obvious corollary is that our ethical rules and standards should be tightened rather than loosened. The "Your Life in Their Hands" series of the B.B.C., however excellent the intentions of those responsible for the programme, showed, we considered, how dangerous such widespread and compelling publicity can be. This was followed by the most odd kind of apologia from those who took a contrary view. The most naive was to measure the "success" of the series in terms of the numbers of people who had looked on apparently with approval. They had evidently forgotten that among the most popular and successful attractions in former times were the public executions at Tyburn. They had forgotten that some of the most successful sales have been, and still are, of pornographic literature. The morbid always has and always will attract. The public has ever hankered after displays of violence, whether it was in the Colosseum of ancient Rome or the bull rings of modern Spain. Those who think they are stripping medicine of its magic and mystery by televising live operations, or films of them, should perhaps ask themselves whether they are not in fact pandering to the same kind of desire.

The public is a partner with the profession in the provision of medical services. Doctors have much to contribute to the life of the community apart from their first task of caring for sick individuals. As practising physicians they should be able to contribute much more than they do to healthy living, as Prince Philip reminded our Canadian colleagues in June. There is plenty of scope to use the facts of modern medicine to illustrate the complexities of human biology in ways that are harmful neither to the public nor to the profession. Neither the G.M.C. nor the B.M.A. has frowned upon doctors' writing articles for the press on professional topics so long as the writers steer clear of advertising their medical wares. As a practising physiologist a doctor is well able to educate the public about the working of body and mind. If it is held, and surely rightly held, that on these and cognate matters it is appropriate for doctors to write signed articles for the press, it might be argued that, with similar safeguards, they should be able to deal with similar subjects through sound and visual broadcasting without the cloak of anonymity. If the B.M.A. and

the G.M.C. ever revise their rules in this respect, they will, it is hoped, urge the need for stringent safeguards in view of the nature of these methods of mass communication.

It is significant that Prince Philip, in his brief address published last week, made a special reference to ethics. In a different context, Dr. Wilder Penfield, moving a vote of thanks to Lord Adrian at Edinburgh in July, made an urgent plea that the medical profession should return to its old traditional behaviour. "We talk so much of medical science," he said, "that we forget to swear the Hippocratic Oath. We never speak of our ethical code, and many who are not of us are ignorant of its existence." And it is interesting to observe that at a time when voices are heard in Britain urging us to adjust our ethical conceptions to meet popular clamour our colleagues in the land of high-pressure advertising are trying to tighten things up. In the *New England Journal of Medicine* of October 15 is published the George W. Gay Lecture on medical ethics delivered at Harvard Medical School earlier this year by Professor J. Howard Means, a lecture to which he gave the title, "Profession or Business?" "Dr. Means," says an editorial in the same issue, "suggests that medicine is showing an alarming tendency to slip from the plane of a profession into the behaviour pattern of the market place . . . a difference in distinguishing ethical from unethical conduct reflects a general social and economic turmoil." The doctor, Dr. Means writes, "sees chiselers and racketeers boring through the otherwise healthy social organism in a great variety of directions"; and he describes the social pressures put upon the doctor, who "is forbidden by all his ethical tradition to engage in advertising, or to solicit patients, which amounts to the same thing. . . ." With courageous criticism of what he has observed in his own country, he says flatly that "organized medicine should abide corporately by its code of ethics as assiduously as it expects its individual members to do. Any double standard in this regard is intolerable." He sees the great danger of the mass media to the doctor who is pushed into public writing or speaking by the institutions with which he is associated—"hospitals, medical schools, and so forth, which have money-raising campaigns under way and wanting to glamorize what they are doing for the advancement of medical science." He recognizes that some of the material used by the mass media for public education are excellent, adding that "some are dreadful."

Dr. Means, recognizing, too, that the more reputable drug houses have gone a long way to raising their ethical standards, nevertheless points out the difficult ethical problems facing doctors subjected to the high-pressure advertising methods of so many others. A new and disturbing tendency in Britain is for drug firms to announce to press conferences the alleged virtues of their own preparations, biological or pharmaceutical. They quickly get what they are after—namely, wide publicity in the national press. Patients thereupon bombard their doctors with requests that they should have the alleged benefits of these new preparations. The medical profession is thus placed in an intolerable position. The proper place to publish the results of this or that prophylactic or remedy is the medical press, and the medical press can assess, on the basis of published evidence, the value of the products marketed by pharmaceutical firms. What makes matters still worse is that some medical men are misguided enough to lend themselves to this undesirable method of advertising. It is ironical that at a time when our colleagues in the U.S.A. are trying to stop this "behaviour of the market place" we should be attempting to imitate it.

DIURETICS UNLIMITED

Until the advent of chlorothiazide parenteral mercurial diuretics were unquestionably the treatment of choice in oedema due to congestive cardiac failure. Millions of injections of mersalyl were given with a minimum of side-effects or toxic reactions. After intravenous administration sudden death due to ventricular fibrillation occurred in a score of patients, but unresponsiveness, sometimes associated with uraemia, was not uncommon, especially when too stringent restriction of sodium intake was coupled with too frequent injections—an undesirable practice largely imported from the United States. But for the inconvenience of parenteral administration, and the advisability of concurrent treatment with ammonium chloride to prevent hypochloraemic alkalosis and unresponsiveness, mersalyl might still be the diuretic of choice.

Acetazolamide, though not destined itself for a star position, pointed the way to a new series of potent diuretic agents that are effective by mouth. Being predominantly a carbonic-anhydrase inhibitor, acetazolamide has a self-limiting diuretic action which ceases when excessive loss of bicarbonate (and potassium) in the urine induces a metabolic acidosis,[1] and it can no longer be recommended for the treatment of oedema.

Chlorothiazide is the first oral diuretic to have a potency comparable with that of mersalyl—

2 grammes by mouth being equivalent to about 2 ml. by intramuscular injection. Its ease of administration, flexibility of dosage, and ready acceptance by the patient have brought an understandable and worth-while advance in diuretic therapy. The only important undesirable side-effect has been a tendency to hypokalaemia due to increased urinary excretion of potassium. This loss of potassium has been attributed to the mild inhibitory action of chlorothiazide on carbonic-anhydrase[2 3]; but this cannot be the whole explanation, because excretion of bicarbonate does not parallel loss of potassium, which is severe only when sodium retention by the kidneys is marked. Furthermore, derivatives of chlorothiazide, which appear to have even less inhibitory effect on carbonic-anhydrase than the parent compound, also increase excretion of potassium. The chief importance of loss of potassium lies in the tendency of patients with hypokalaemia to develop digitalis intoxication. This is less likely to occur now that the practice in early clinical trials[4] of giving too much chlorothiazide too frequently has been abandoned in favour of intermittent treatment, combined, if the patient is eating poorly or the oedema takes more than ten to fourteen days to clear, with supplements of potassium on days when the diuretic is not given.

A number of derivatives of chlorothiazide have been introduced recently, and doubtless there are others yet to come. The practitioner is spoilt for choice and may feel somewhat bewildered. The first derivative to be introduced was hydrochlorothiazide,[5-7] and this has been now followed by hydroflumethiazide[8-10] (hydrofluorochlorothiazide). These compounds, on a weight-for-weight basis, are more potent than chlorothiazide, but this is of no great advantage unless there is some superiority over the parent compound in the pattern of diuresis produced. Both hydrochlorothiazide and hydroflumethiazide have little or no inhibitory effect on carbonic-anhydrase, and so it was hoped that there would be no increased excretion of potassium in the urine. This has not proved to be the case with hydrochlorothiazide[11 12] nor, as reported by Drs. J. H. Jones and J. Verrier Jones elsewhere in this issue, with hydroflumethiazide, which induced a fall in the serum potassium below normal in 16 out of 20 patients treated. Both these derivatives should be given intermittently and supplements of potassium be provided in the same circumstances as are necessary with chlorothiazide.[8 10]

Chlorothiazide, or one of its derivatives, is the diuretic of choice in almost all cases of oedema both for initial therapy and, because of flexibility in dosage, for maintenance treatment. No one particular compound has any outstanding therapeutic advantage over another, and the practitioner is likely to use that with which he personally is most familiar. Other diuretics now come in the "also-ran" category, with mersalyl still of value in the occasional unresponsive patient or in refractory cases to potentiate the action of chlorothiazide.

[1] Counihan, T. B., Evans, B. M., and Milne, M. D., *Clin. Sci.*, 1955, **13**, 585.
[2] Slater, J. D. H., and Nabarro, J. D. N., *Lancet*, 1958, **1**, 124.
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[4] Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F., ibid., 1958, **1**, 120.
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[9] Kennedy, A. C., Watson, W. C., and Cunningham, C., ibid., 1959, **2**, 309.
[10] Blagg, C. R., ibid., 1959, **2**, 311.
[11] Sackner, M. A., Wallack, A. A., and Bellet, S., *Amer. J. med. Sci.*, 1959, **237**, 575.
[12] Bartorelli, C., Gargano, N., and Zanchetti, A., *Schweiz. med. Wschr.*, 1959, **89**, 331.

BED REST IN ACUTE NEPHRITIS

As scientific knowledge advances, and we rely more on the scientific method than on clinical impression to assess the effects of treatment, so more of our long-cherished beliefs are being questioned and discarded. One of these concerns the value of rest in bed for a wide variety of conditions in child and adult. Until recently few doctors have questioned the rationale of bed rest. Yet it is difficult to understand why it should be thought that a child would recover from any of a wide variety of ailments more quickly if he sits up in bed than if he sits or plays in his bedroom—or any other room if it is warm.

It has long been held that children with acute nephritis should stay in bed until most of the signs of renal disease have disappeared—and that, for many children, meant many weeks in bed. It has long been known that albuminuria often follows severe exertion. E. P. Alyea and H. H. Parish[1] showed that not only albumin but large quantities of red blood cells and casts appeared in the urine of most athletes after rowing, swimming, lacrosse, track events, and football. They suggested that it might be unwise for a person who had had nephritis to indulge in severe exercise. This might be thought to have some bearing on the duration of bed rest advisable in acute nephritis.

[1] Alyea, E. P., and Parish, H. H., *J. Amer. med. Ass.*, 1958, **167**, 807.
[2] Rudebeck, J., *Acta med. Scand.*, 1946, Suppl. 173.
[3] Äkerren, Y., and Lindgren, M., ibid., 1955, **151**, 419.
[4] —— —— ibid., 1956, **154**, 245.
[5] McCrory, W. W., Fleisher, D., and Sohn, W. B., *Amer. J. Dis. Child.*, 1958, **96**, 576.
[6] —— —— —— *Pediatrics*, 1959, **24**, 395.

On the other hand several workers have shown that early ambulation in acute nephritis in children is harmless. J. Rudebeck[2] described in his monograph how early rising appeared to do no harm. Y. Äkerren and M. Lindgren[3 4] later gave an account of a controlled study in which 29 children were allowed to get up as soon as macroscopic haematuria disappeared, and 28 were kept in bed until the erythrocyte sedimentation rate and Addis count were normal. Twelve children in the latter group had to be kept in hospital for more than three months. There was no difference in the rate of recovery in the two groups, and all children recovered completely.

More recently W. W. McCrory and colleagues[5 6] reached a similar conclusion in a study of 35 children, 8 girls and 27 boys, aged 2 to 12 years. All were kept in bed in the acute stage, but as soon as acute symptoms had subsided, and irrespective of the urinary or blood findings, they were gradually allowed to resume full activity, so that they were all attending school within two months of the onset, and all taking part in normal physical activity within two or at the most three months of the onset. The longest period of bed rest for any child was one month. The nephritis seemed to be of average severity. None showed any adverse symptoms or signs as a result of early ambulation, and 29 out of 35 had a normal Addis count within a year of the onset; all but one had a normal count, and could therefore be considered to have recovered fully, two years after the onset. The authors presented this work before the American Pediatric Society, and in the ensuing discussion several paediatricians gave their own experience, which was in complete agreement with that of McCrory and his colleagues. One of the speakers, J. N. Etteldorf, for example, had similarly good results with 41 children suffering from acute nephritis. They were allowed up as soon as they reached the hospital.

It would seem therefore that children with acute nephritis can safely be allowed to get up much earlier than has been the practice in the past. One might arbitrarily say that they can get up and about as soon as haematuria visible to the naked eye has disappeared. It is bad for psychological reasons for a child (or anyone else) to stay in bed longer than is necessary. It weakens the patient and inevitably prolongs the convalescent period. In the case of school-children prolonged bed rest, when insisted on without proper medical grounds, causes an unwarrantable interference with schooling. There seems to be nothing against early ambulation for children with acute nephritis—and there is a lot for it.

A NEW PENICILLIN

It was publicly announced on October 26, and widely reported in the daily press, that a new penicillin has now been produced which can be administered orally, and that "its effectiveness is twice as great as that of penicillin V." This is the first therapeutic consequence of the isolation in the Beecham Research Laboratories of the penicillin nucleus, 6-aminopenicillanic acid. The new therapeutic compound is the potassium salt of 6-(α-phenoxypropionamido) penicillanic acid, to be known as "broxil," and an advertisement of it appears in this issue.

The only source of information on the drug's action available to us is a brochure of 18 pages provided by Beecham Research Laboratories Ltd., concluding with a "bibliography" of 18 items, every one of which is a "personal communication." It describes a series of mainly laboratory studies from which it emerges that the advantage of the new penicillin over penicillin V is that of better absorption. Average blood levels in 20 normal subjects, ½, 1, 2, 4, and 6 hours after a single oral 250-mg. dose were 1.7, 1.6, 0.8, 0.1, and 0.01 μg./ml. for penicillin V, and 3.7, 3.8, 0.9, 0.2, and 0.01 for broxil (the assay method is not described, but presumably a separate standard was used for each drug). As regards *in vitro* activity, comparative data for a short range of bacterial species are presented, including values for penicillins G and V. There is no evidence here of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both: this applies to all varieties of streptococci tested. As regards staphylococci, two strains in this table are shown as equally sensitive to all three penicillins; reports from individual workers mention that some strains were "somewhat" or "slightly" more sensitive to broxil than to V or G, but it is also said of penicillinase-producing strains that "in general, the organisms were resistant to both forms of penicillin." This must be taken to mean that broxil is destroyed by staphylococcal penicillinase, although the very simple experiment which would decide whether this is so is not reported as having been done. Broxil has been given with satisfactory results to about 500 patients. It is mentioned that 9 of them gave histories of allergy to penicillin, and only one of these reacted in this way to broxil, but other literature from the manufacturers contains the statement: "Broxil should not be given to penicillin-sensitive persons."

The issue of the *Journal* of October 31 contains (p. 880) a brief report of a communication by Dr. G. N. Rolinson, of the Beecham Research Laboratories, to the Annual Clinical Meeting at Norwich, in which he said that new penicillins had been developed, certain of which would not provoke reaction in sensitized patients, which would be active against a much broader bacterial spectrum, including Gram-negative bacteria, and "would be stable against penicillinase and would therefore be active against the staphylococci which were at present resistant to penicillin G by virtue of their ability to produce penicillinase." It is much to be hoped that

penicillins with these very desirable properties will eventually be forthcoming, but we feel it most necessary to inform the medical public that, according to the information provided by Beecham's, broxil possesses none of them.

RADIOACTIVE CONTAMINATION OF FOOD

In 1957 the Agricultural Research Council became responsible for investigating the contamination of food and agricultural land by radioactive substances. The first report from the Radiobiological Laboratory set up to carry out the investigations has recently been published,[1] and records the concentrations of calcium, stable strontium, and the radioactive isotope strontium-90 found in milk, potatoes, flour, and green vegetables.

Strontium-90, which has a half-life of 28 years, is deposited with calcium in newly formed bone and will irradiate bone and bone-marrow, the intensity of the irradiation depending upon the concentration of strontium-90. This concentration is determined principally by the ratio of strontium-90 to calcium in the whole diet. Thus the measurements on which the radiation hazard has been estimated have been recorded as micro-micro-curies of strontium-90 per gramme of calcium ($\mu\mu$c/g. Ca). On evidence available in 1956 the Medical Research Council[2] advised that the maximum allowable concentration of strontium-90 in the bones of the general population should be 100 $\mu\mu$c/g. Ca. But if the general level were to show signs of rising greatly beyond one-tenth of this, the implications would have to be urgently considered.

The Agricultural Research Council reports an average of 6 $\mu\mu$c/g. Ca in the United Kingdom diet, and it was considered unlikely that the diet for any large number of people would contain more than 10 units. Milk was found to contain an average of 7, cheese 7.7, cabbage, brussels sprouts, and similar vegetables 8.7, and flour from all sources 16 $\mu\mu$c/g. Ca. When allowance was made for the relative amounts of these foods consumed daily, it was found that, in the average daily intake of food, milk accounted for 54% of the strontium-90, flour 12%, cheese 11%, vegetables 10%, meat 4%, drinking water 4%, fruit 3%, eggs 0.6%, and fish 0.2%. Because white bread is made from flour to which uncontaminated calcium has been added, whereas much wholemeal bread contains no added calcium, and since the strontium-90 content of bran is seven times that of white flour, the average daily intake of strontium-90 per gramme of calcium would be increased from 6 $\mu\mu$c to 9 $\mu\mu$c if white bread in the diet were replaced by wholemeal bread.

In some areas values of strontium-90 up to six times the average levels in the United Kingdom were found. On the pessimistic view of a person selecting the most highly contaminated food from these areas for his diet, the report estimates that his intake of strontium-90 would be 23 $\mu\mu$c/g. Ca, stressing at the same time that the probability of this occurring is remote.

In a paper presented at the recent British Association meeting in York[3] W. V. Mayneord, R. C. Turner, and J. M. Radley gave some interesting measurements of the amount of radium and thorium contained in various foodstuffs. Using a sensitive and elegant counting technique which they had developed for the purpose, they showed that, on a diet rich in carbohydrates, a person may ingest daily about one-quarter as much radium and thorium as he has permanently fixed in his body. Fruit and vegetables, animal protein, milk, and fish all showed very low activity, while flour, cereals, and nuts were high. The Brazil nut yielded the highest α-particle activity of all the foodstuffs tested—4 oz. (113 g.) of these nuts containing as much radium and thorium as the entire human body. The authors consider the interesting question why the concentration of radium and thorium in a normal person should remain relatively constant throughout life in spite of a large daily intake, but do not provide an explicit answer.

They also compared the importance of ingested strontium-90 due to fall-out from weapon tests with that of radium and thorium taken in food, considering the contribution from strontium-90 to be negligible. This conclusion received great prominence in newspaper reports, but the authors referred only briefly to it. A comparison of the long-term effects of different radioisotopes must depend not on relative daily intakes but on the amounts retained in the body, and Mayneord and his colleagues have shown that the surprisingly high intake of radium and thorium in normal diets does not lead to a progressive increase of the radium burden in the body. Yet levels of strontium in the body are rising in spite of its relatively low activity in food. It would seem that further careful studies of these matters, for which the measurements presented in the paper could serve as an excellent model, will be required before we shall know with any certainty what effects, if any, can arise from very low levels of radioactivity in the body.

[1] Agricultural Research Council Radiobiological Laboratory, *Strontium-90 in Human Diet in the United Kingdom 1958*, Report No. 1, 1959, H.M.S.O., London.
[2] Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*, 1956, cmd. 9780, H.M.S.O.
[3] Mayneord, W. V., Radley, J. M., and Turner, R. C., Address to the British Association, September, 1959.

VISUAL DEFECTS IN CHILDREN

Striking differences in the incidence of some defects in children have been recorded in different parts of the country. The Chief Medical Officer of the Ministry of Education devoted a chapter to discussing this in his last report reviewing fifty years' achievements in the school health service.[1] That such variations exist has been known for many years, and, while it is clear that

[1] Report of the Chief Medical Officer of the Ministry of Education for the year 1956 and 1957. *The Health of the School Child*. 1958. H.M.S.O., London.
[2] Hampshire County Council, *Annual Report of the Principal School Medical Officer for the year 1958*, p. 11.

some of them reflect little more than differences in the methods of recording the findings, there has always been the possibility that there are real differences too. The ophthalmic findings in particular have attracted attention.

Thus in England visual defects have been recorded for 46 per 1,000 children examined by county council authorities, against 53.7 for county boroughs and 59.8 for the London County Council. When the analysis is carried further it is found that this distinction between county councils and county boroughs as groups breaks down and that the differences between authorities within each group can be very wide indeed. Thus the Leicester County Borough reports a rate of 94.2 visual defects per 1,000 children, while nearby Nottingham County Borough has a rate of 29.8. For squint, the Leicester County Borough gives a rate of 27.9 per 1,000, while the Leicester County Council and Northants County Council give rates of 6.5 and 2.3. It would seem that both in the measurement of visual defect and in the assessment of squint there must be considerable variations between different assessors.

This problem is not new; it first emerged forcibly with the registrations of ophthalmia neonatorum. Thus, at a time when the national rate of notification ran at fewer than 10 per thousand births, Birmingham recorded an incidence of about 50–60. What is more relevant is that within the same area there are fluctuations not readily explained by changes in staff or in methods of examination. For instance, the annual report for 1958 of the principal school medical officer to the Hampshire County Council[2] shows a rise in the incidence of squint from 12.1 per thousand children examined at periodical medical examination in 1949 to 25.1 in 1958, with a fairly uniform rise in between, but even so it is likely that a greater awareness of the significance of minor ocular imbalance has led to the more frequent reference of children for treatment of squint. Certainly the development of squint departments at many hospitals will have helped this. With increasing uniformity in methods of examination, in standards of staff, and in facilities available, the apparent discrepancies that have been plaguing school authorities for so many years are likely to become less persistent. There is certainly no justification for blaming television and suchlike developments for ill-substantiated increases in the incidence of visual defects.

TREATMENT OF VENEREAL DISEASES OUTSIDE HOSPITALS

The venereal diseases flourish in times of war and economic depression, and the attendances of new patients at clinics reached a peak in 1946. However, since penicillin became generally available and was such a powerful drug against the organisms causing syphilis and gonorrhoea, it seemed possib'e that these diseases would cease to be a major problem, and their eradication was thought by many to be only a matter of time. But these hopes proved illusory, and, as A. J. King[1] showed in a recent Malcolm Morris lecture, venereal infections, far from being dying diseases, are still a menace to public health. It is true that there was a dramatic decline in the incidence of early infectious syphilis in the immediate post-war years, but this trend was arrested in 1955 and there has been no marked improvement since then. The figures for the attendance of patients with gonorrhoea also showed a steep fall from 1946 until 1955; since then they have increased substantially each successive year, and it has become clear that this disease is by no means under control. Some strains of gonococci are now partially resistant to penicillin, and this, together with the influx of coloured immigrants within recent years, may have contributed to the worsening of the situation.

The data on which figures of the incidence of venereal disease are compiled are derived from the returns of patients attending V.D. clinics in hospitals. This only shows part of the picture, since an unknown number of patients seek treatment from general practitioners and others outside the hospital service. An attempt has been made by the Venereologists Group Committee of the B.M.A., in association with the British Co-operative Clinical Group, to estimate the proportion of patients with venereal diseases who are treated outside clinics, and the results of the survey have recently been published.[2] Questionaries were sent to all members of the B.M.A. in four representative areas (Southampton, Leeds, Norfolk, and part of London) asking them for the number of cases treated by them in 1956.

The response to the questionary was rather disappointing, since only 562 replies were received from the 1,743 doctors to whom it was sent. Allowing for those who were not in clinical practice, about a quarter of those who answered had treated cases during the year. Analysis of the returns showed that the numbers of patients obtaining treatment outside the clinics in the areas surveyed amounted to 24.8% of those attending the clinics with syphilis (all stages) and 14.9% of those attending with gonorrhoea or non-gonococcal urethritis. These percentages are minimum ones, and if the results hold good for the rest of the country it seems clear that the "official" figures based on clinic returns substantially underestimate the true total.

If a patient wishes, he should be able to seek advice and treatment from his own doctor rather than go to a clinic, but it is important that he should receive the same high standard of investigation and treatment as he would at a hospital clinic. The individual patient represents a link in a chain of infection, and contact tracing is one of the most important parts of the work at V.D. clinics: each fresh case of venereal disease presents an opportunity to bring infected contacts under treatment and thus to diminish the reservoir of infection in the community. Unless this ideal is pursued, the venereal diseases will continue to be a menace to the public health despite the effective methods of treatment at our command.

[1] King, A. J., *Lancet*, 1958, **1**, 651.
[2] *Brit. J. vener. Dis.*, 1959, **35**, 111.

Drug Treatment of Disease

CORTICOSTEROIDS IN TREATMENT OF SKIN DISEASES

I. SYSTEMIC TREATMENT

BY

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In 1953, when the supplies of steroid hormones were still meagre, a memorandum from the Ministry of Health mentioned several diseases for which priority might be given. This short list contained several diseases affecting the skin, and the promise of those days has been fulfilled. It is hardly too much to say that in respect of the more serious disorders the face of dermatology has been changed by this new method of treatment.

The steroids chiefly used in the treatment of skin diseases are A.C.T.H., cortisone, prednisone, prednisolone, and, more recently, triamcinolone. So far as their therapeutic efficiency is concerned there is not a great deal to choose between them, though of course the actual size of dose varies. More important differences are in side-effects and complications. At the present time prednisone is the one chiefly used, though perhaps before long triamcinolone will emerge as being somewhat superior. For purposes of simplicity the dose of steroids referred to below refers always to prednisone. Although reference is made to a total daily dose, it is the usual practice to divide this into two or three doses during the day.

Dangers of Steroids

The dangers attendant upon this treatment are very real, and before embarking upon steroid therapy it is essential to ascertain so far as possible the prospect of complications arising. *X*-ray examination of the chest should always be done to exclude latent tuberculosis; blood pressure should be taken and urine tested for albumin and sugar. Whenever there is a history suggestive of peptic ulceration, this should be looked into, and barium-meal examination made. Very often admission to hospital is necessary for the purpose of these investigations and for the start of treatment and initiation of maintenance therapy. During treatment many complications may arise; it is essential that these patients be seen by the doctor at intervals of not less than a fortnight and considerably more often in the early stages before an adjustment of maintenance dose has been made. Although, therefore, great benefits may be derived from this form of treatment, it is not one which should ever be embarked upon lightly. Fatalities resulting from the treatment are, in the present state of our knowledge, inevitable, and the price paid by the patient and by his doctor can be high.

Effective Dosage

If all these preliminary investigations give negative results, treatment may be started and an effective dose should be given at the onset. Failure to respond to the usual doses sometimes results from half-hearted under-dosage at first.

The termination of therapy often requires some skill, because it is common for the original disorder to recur, at least in part, if treatment is stopped suddenly. It is, therefore, nearly always necessary to reduce the dose slowly. When doses of 40 or 50 mg. daily are being given, a reduction of 5 mg. two or three times a week may be satisfactory, but when the daily dose is in the region of 20 mg. or less it is often best to reduce by only 1 mg. a day. Even when the dose is reduced as slowly as this there may be some tendency to relapse; this does not necessarily indicate that the dose should be increased again, for after a few days on the reduced dose a minor relapse may well subside and permit further reduction. It is in this way that the level of maintenance treatment is eventually determined.

In most disorders in which maintenance is required, it is probably best to give a dose which does not entirely suppress symptoms. If very slight manifestations of the disease continue it is perhaps the best indication that, though the disorder is under control, an unnecessarily large dose of steroid is not being given. In these circumstances more severe relapse of the original disease may occur if there is any added stress. A minor illness such as coryza may impose sufficient stress to cause a relapse of a disorder which has hitherto been nicely under control. At times such as these the maintenance dose may have to be increased for a few days.

As will be seen below, there are a number of self-limiting disorders in which a short course of treatment may be given lasting three or four weeks. Many of the complications of steroid treatment may occur at the beginning of treatment, so that even such a short course should not be undertaken without adequate investigation beforehand. Sometimes the results are not so good as expected, and there is a tendency for a treatment which was originally intended to last a month or so to run into a considerably longer period, perhaps with unfortunate results. Before steroid therapy is begun, its object and limits should always be clearly defined. If the original intention has been to give a short course of four or five weeks and it is then continued beyond that time, the whole position should be reviewed and a fresh plan of campaign evolved.

A final general point of great importance is that steroid therapy should never be given as a substitute for accurate diagnosis.

THE BULLOUS DISEASES

Pemphigus vulgaris and the related disorders pemphigus foliaceus and vegetans occupy a prominent place among skin diseases. They are striking, disabling, extremely unpleasant, and dangerous; they carry perhaps the highest mortality of any cutaneous disease, being fatal in the majority of cases. Few treatments other than steroids have any value, and none are reliable. The steroid hormones, however, have a dramatic effect and quickly suppress the eruption in the great majority of cases. Without this treatment the

disease is so dangerous that steroids are imperatively indicated as soon as the diagnosis is made. There is some reason to suppose that if treatment is delayed the response may eventually not be so good, and this occurs also if initial dosage is too small. Once the diagnosis of pemphigus is made, therefore, there need be no delay. These patients may require large initial doses, often up to 100 mg. daily and sometimes 150 mg. or even more before the eruption of blisters has completely ceased. So dangerous is the disease, however, that there should be no hesitation in giving these large doses in order to achieve the initial effect; and at the same time contra-indications have to be met by countermeasures rather than by withholding steroids.

The usual practice is to start dosage at 40 or 50 mg. of prednisone daily, and unless fresh blisters cease to form within three or four days the dose is rapidly increased. In this way the production of blisters can usually be checked in the course of ten or fourteen days, and once this stage is reached one may at once start to reduce the dose. This should be done cautiously in steps of 5 to 10 mg. weekly, the occurrence of fresh blisters being an indication that the reduction of dose is proceeding too quickly. Eventually, after a period of several weeks, it is usually possible to reach a maintenance dose which may be in the region of 15 mg. a day, but is sometimes less.

The results of this treatment are that the mortality of pemphigus has been reduced to about 30% or less of its previous level. Some patients die now because the disorder cannot be brought under control even with the largest doses. Others die from complications of treatment or from intercurrent diseases. Many of them are elderly.

Other Bullous Diseases

Most other bullous diseases show some response to steroids. One of the commonest is *pemphigoid*, which affects chiefly elderly people. However, the disorder is not so serious as true pemphigus, and in these elderly patients contraindications are so often present that it may be wiser to avoid steroid therapy.

Stevens–Johnson Syndrome

There is a certain mortality from this disease, but most often it is self-limiting, though unpleasant. The administration of steroids can always be expected to produce a striking improvement and to hasten recovery. The initial dose is usually in the region of 40 to 50 mg. of prednisone daily and this may quickly be reduced once the symptoms are abating. The total period of treatment will usually last not more than three or four weeks.

THE ECZEMA-DERMATITIS GROUP

This group comprises the main bulk of cases in which steroids are indicated.

Exfoliative Dermatitis

Exfoliative dermatitis affects mainly the middle-aged and elderly. In some cases it is the extension of a pre-existing skin disease, particularly of more or less localized eczema; in other cases it may be provoked by a reticulosis or by drug intoxication; in many cases it occurs as a primary condition and without ascertainable cause.

The cutaneous eruption is accompanied by a deterioration in the general health, both physical and mental. Younger patients are usually able to withstand the disorder and recovery follows after a period of months or years. In elderly patients, however, the strain may be too great, and death may occur from exhaustion or from intercurrent disease, particularly of the respiratory system.

In the great majority of these cases the skin can be returned completely to normal by steroid treatment. The initial dose needs to be a substantial one, usually 35 to 45 mg. of prednisone a day, but it is never necessary to give the high doses which may be required for pemphigus. In the course of a few days irritation ceases, subcutaneous oedema diminishes, and in ten or fourteen days the skin has resumed a normal appearance. The dose is then gradually reduced to a maintenance level, which is usually 10 to 15 mg. a day. In favourable cases this maintenance dose can be continued with complete suppression of the disorder until eventually natural recovery makes further treatment unnecessary.

The decision to undertake steroid therapy for exfoliative dermatitis is often an extremely difficult one. In younger patients the threat to life is small and one must decide whether disability and discomfort warrant a treatment which in itself carries a mortality. In the older patient the associated diseases which constitute the principal danger are often also contraindications to steroid therapy. These elderly patients often have chronic respiratory, cardiovascular, or mental disorders which threaten life whether they are treated with steroids or not. Often one feels that without treatment they are likely to die before their skin has recovered and that the risks of steroid therapy are worth taking in order to ensure that the rest of their life will be tolerable even if it is curtailed. Even in retrospect it is often difficult to decide whether it was right to embark upon steroid therapy, and certainly the decision cannot be taken without very careful thought and appraisement of imponderable factors.

Acute Eczema

Acute contact eczema, and the sensitization eczema which sometimes complicates varicose dermatitis and other localized conditions, are distressing and disabling but essentially self-limiting and present no threat to life. In severe cases systemic steroid therapy is valuable given over a short period. 30 to 40 mg. of prednisone per day will usually suppress the acute reaction in a week or so, after which the dose may be immediately tapered off, so that a total period of four or five weeks' treatment is envisaged.

Atopic Eczema

This disorder, also known as disseminated neuro-dermatitis and Besnier's prurigo, occurs in all degrees of severity and may be accompanied by asthma, hay-fever, and other allergic manifestations. The symptoms can always be removed with steroid treatment. The disease is essentially inborn and can hardly be susceptible of cure, so that the benefits of steroid therapy will last only so long as the treatment is continued. These patients are, however, subject to occasional severe relapses, and sometimes at these periods steroid therapy may be justified. Apart from this there are a very few extremely severe cases in which the patient's life is a misery and both work and pleasure are impossible. In these rare cases steroid therapy maintained over months or years is justified. It should be emphasized, however, that these cases are few and far between. The dosage required for suppression of symptoms is usually in the region of 25 or 30 mg. of

prednisone daily—larger than the maintenance dose required for many other conditions. The attendant risks, therefore, must be carefully balanced against the severity of the illness.

In this condition, as in most chronic disorders, it is undesirable to give the patient a demonstration of the great benefits of steroid therapy if it is not proposed to continue them. Patients who have had a glimpse of the respite such treatment may give are only liable to be the more unhappy if afterwards this treatment is firmly, though wisely, withheld. There is, of course, a tendency to shake off this disorder as age advances. It is, however, only in the most serious cases that treatment would be given, and these are the ones where spontaneous recovery is unlikely. Occasionally in infants severe atopic eczema may be treated in this way.

Drug Eruptions

Most drug eruptions are comparatively short and sharp and are likely to subside in the course of a few days. For these, systemic steroids are not indicated. Certain drugs, however, are likely to produce eruptions of much longer duration. Notable examples are the eruptions produced by mepacrine and by gold. Cases of this sort may be treated by the method outlined for acute eczemas. The response to treatment is usually excellent and complete recovery takes place in a few days. As the dosage has to be reduced slowly, the duration of treatment is usually about a month or six weeks.

Lupus Erythematosus

Steroids do not enter into the treatment of fixed, localized, cutaneous lupus erythematosus. Although most cases of the disseminated type are in the hands of the general physician, they occasionally come under the care of the dermatologist. The symptoms of disseminated lupus erythematosus can usually be partly or completely suppressed by steroids, but it is not certain how much the eventual outcome of the illness is influenced. D.L.E. is a disorder or syndrome which presents in many guises with a great variety of symptoms, and which runs an extremely variable course. Although it may not be difficult to assess the influence on symptoms, it is often difficult to know whether the course and the development of remissions have been much altered by treatment. While, therefore, steroid therapy is indicated for the relief of severe and intractable symptoms—provided that other safer methods of treatment have first been tried—opinions are much divided on whether it should be given in the general treatment of the disease.

Dermatomyositis

This rare disease also appears in all degrees of severity and runs a very variable course. In all but the mildest cases steroid treatment is usually given, but results are difficult to assess. Large doses may be required.

There are several other disorders in which a response to steroids can be obtained, but because of their relative mildness the risks of that treatment are not often justifiable. In this category are lichen planus, aphthous ulcers of the mouth and genital region, and a number of rarer disorders. It is not often that steroid therapy is indicated; when it is given, its effects are apt to be temporary, and we are faced with the dangers of indefinite maintenance treatment in exchange for a harmless, uncomfortable, but seldom disabling disorder.

(To be concluded.)

B.M.A. ANNUAL CLINICAL MEETING

NORWICH, OCTOBER 22–25

The final count of those who registered at the Association's Second Annual Clinical Meeting at Norwich last month was 415, and to this excellent total must be added quite an appreciable number who did not succeed in registering. Of the 415, over 200 came from outside East Anglia. All who attended the Meeting would acknowledge their debt to the local officers—Mr. J. M. RIDLEY THOMAS (chairman), Dr. R. H. SCOTT (honorary general secretary), Dr. A. BAITY SHAW (honorary science secretary), Dr. A. L. REYNARD (colour television), and Dr. B. M. MAXWELL (transatlantic clinical conference)—and to Dr. P. R. WILSON, the chairman of the Meeting's committee of management, who between them did so much to make the Meeting a success.

The first half of the Meeting was reported in our last week's issue (*Journal*, October 31, pp. 878–882). The rest of the report appears below.

SECOND GENERAL SESSION

Professor J. S. MITCHELL (Cambridge) took the chair at the Second General Session on Saturday morning, at which there were three guest speakers.

Psychiatry and Psycho-analysis

Dr. W. MAYER-GROSS (Birmingham) discussed psychiatry and psycho-analysis. Although only 20 years had elapsed since Freud's death, his doctrines and teachings had made a profound impact on everyday life and on modern scientific medicine. They still formed a basis on which the psychoneurotic patient might be treated. It was important, therefore, that both the family doctor and the specialist in other branches of medicine should be able to understand the reaction of his patients to Freudian doctrines and the bearing they had on the treatment of psychiatric disorders.

The training of sufficient psycho-analysts presented formidable problems, and Dr. Mayer-Gross doubted if the shorter periods of training advocated by Balint at the Tavistock Clinic were sufficient to give the background of knowledge necessary to make treatment adequate. However, any doctor with patience, tolerance, wisdom, sympathy, and maturity would soon win his patients' trust, and by reassurance, explanation, and planning for the future be able to correct the majority of psychosomatic manifestations. He should, at least, be able to tide him over until a spontaneous remission of symptoms occurred. There was indeed little evidence that more complex, expert, prolonged psycho-analysis achieved results in any way better than those obtainable by simpler methods of psychotherapy.

Indications for Therapeutic Abortion

The indications for therapeutic abortion were described by Professor T. N. A. JEFFCOATE (Liverpool) on the basis of a 10-year obstetric experience at three Liverpool hospitals. The need for termination occurred only rarely: under present-day conditions probably not more frequently than one in every 1,000 pregnancies. He estimated that the problem would arise only once in every 25 years in an average practice. It should be realized that the operation was a serious one, carrying an appreciable mortality and morbidity, and inducing considerable physical and

psychological stress upon the mother whereby a considerable proportion were left with a permanent physical defect or with feelings of guilt.

Of the indications for which Professor Jeffcoate and his colleagues had advised therapeutic abortion, heart disease, phthisis, renal failure, and hypertension were those most commonly encountered; termination was less often required for potential foetal abnormalities, psychiatric disorders, respiratory insufficiency, or breast cancer. With the advent of chemotherapy therapeutic abortion in pulmonary tuberculosis had hardly ever been necessary in the last five years, save for reasons of pulmonary insufficiency, a condition which could also arise in patients with a severe dorsal kyphoscoliosis. The obstetric indications such as hyperemesis, a common indication 20 years ago, had virtually disappeared from consideration. The incidence of

[George Gregory, Norwich

Professor T. N. A. Jeffcoate speaking at the Second General Session.

termination in psychiatric disorders varied enormously in series from different hospitals. It should be undertaken only rarely, and then in close consultation with a psychiatric colleague. Therapeutic abortion for potential foetal abnormalities induced by virus infection early in pregnancy, rhesus auto-immunization, or because of previously inherited physical defects, could be legally justified only if it could be shown that worry about the probability of foetal abnormality was impairing the mother's health.

Therapeutic abortion had to be justified in every individual case, and could not be said to be always indicated in a particular disease. Even if medical indications were strong and confirmed by a second opinion, the situation could only be explained to the patient and her husband and a final decision left to them. The speaker was against changing the law on therapeutic abortion, as he thought it was sufficiently flexible to be applicable to most patients' needs.

In reply to questions, Professor Jeffcoate re-emphasized the rarity of the need for termination in psychiatric disorders and said that in his experience caesarean section could not be relied upon to reduce the risks of delivery in heart disease or pulmonary insufficiency. He thought further evidence would have to be collected to decide whether gamma-globulin given early in pregnancy protected the foetus, or whether influenza during the first trimester produced foetal damage.

Therapeutic Applications of Radioiodine

The present status of radioiodine in the treatment of thyroid disease was expertly reviewed by Dr. E. E. POCHIN (London). The profound benefits induced in thyrotoxicosis, thyroid carcinoma, and invariably in intractable angina of effort had made it the most useful and most widely applied isotope in clinical medicine to-day. The highly selective uptake of iodine by the thyroid gland made it possible to give high levels of irradiation to the thyroid without exposing the patient to the general dangers of irradiation.

In thyrotoxicosis, radioiodine was the treatment of choice in the elderly patient, the thyro-cardiac patient, and the younger patient in whom other treatments had failed or were inapplicable. This included recurrence of toxicity after thyroidectomy or sensitivity to antithyroid drugs. Dosage, based on previous tracer studies and clinical estimation of the size of the gland, was still inexact, and some patients were rendered myxoedematous by therapy or might require two or three treatments to suppress symptoms. The fear that radiation might induce thyroid carcinoma or leukaemia had to date prevented the use of radioiodine in young patients, but review of experience of the treatment over 15 years had as yet shown no evidence that the prevalence of either disorder was increased in patients treated.

In thyroid cancer, radioiodine in large dosage commonly offered a clinically valuable, and possibly curative, treatment in the patient with a surgically inoperable carcinoma. The efficacy of the treatment again depended on the ability of the gland and its secondaries to take up radioiodine. Best results were obtained in the well-differentiated papillary or follicular carcinomata. It was necessary, therefore, in planning treatment to perform a gland biopsy. If the gland was judged operable, surgery was advised; if anaplastic histologically, radiotherapy was used. In the inoperable well-differentiated growth, the thyroid was first ablated with a large dose of radioiodine, which often rendered previously refractory secondaries sensitive to a second course of treatment. Therapy was pursued until no further uptake of radioiodine in the body could be administered. Excellent short-term results had been obtained, but a 20-year follow-up would be necessary before cures could be claimed.

In reply to questions Dr. Pochin stated that radioiodine fared no worse, and possibly better, than other treatment in the patient with severe exophthalmos. It could be used in the elderly patient with a toxic nodular goitre, provided carcinoma had been excluded by gland biopsy. He had no evidence to suggest that the heavy irradiation used in thyroid cancer had damaged the parathyroid glands, but in some patients persistent salivary gland enlargement and reduced salivation had followed therapy. He thought that radioiodine should be used post-operatively in patients with thyroid carcinoma only if excision of the gland was considered to be incomplete.

PANEL ON HEAD INJURIES

Under the chairmanship of Dr. K. A. LATTER (Norwich) a well-attended panel discussion on head injuries was led by Sir CHARLES SYMONDS (London) and Mr. WALPOLE LEWIN (Oxford).

Dr. LATTER, in opening the discussion, stressed the importance of head injuries in view of the steadily increasing numbers of road accidents. He asked what advice the panel could give to the general practitioner confronted with a head injury. In reply, Sir CHARLES SYMONDS said the practitioner should obtain as accurate an account as possible of the circumstances of the injury, and stressed that an adequate examination of the patient soon after the accident was of considerable importance. This should include an assessment of the patient's state of consciousness and also, so far as circumstances permitted, a neurological examination. In subsequent management, such information was of great help, for it was vital to know if any deterioration in the state of consciousness had occurred or if physical signs not present initially had made their appearance.

The panel then considered which cases of head injury should be admitted to hospital. Mr. LEWIN emphasized that it was most difficult to predict what would happen in the 24 hours after a head injury, and observation over this

period was essential. Such observation was sometimes possible at home, depending upon circumstance, but, where it was not, admission to hospital might be required. Both he and Sir Charles felt that in anyone who had sustained definite concussion it was wise to admit the patient for 24 hours. The panel were also asked which cases should have an *x*-ray examination, and again they agreed that this should be performed in every instance where there had been definite concussion. Mr. LEWIN stressed that there was no clinical way of diagnosing a fracture, and Sir CHARLES pointed out that it was important not to miss a fissured fracture running into the frontal sinuses in view of the liability to meningitis. Vomiting after head injury was sometimes a problem, and inhalation of vomit might lead to hypoxia being an additional problem. If not contraindicated for other reasons, such as spinal injury, cases should be transferred to hospital lying on their sides.

Dr. U. M. DICK inquired about the management of children after concussion. Sir CHARLES replied that anyone after concussion should be at rest—not necessarily in bed—for about 48 hours before physical or mental activity was allowed, and that after that activity should be graded by symptoms. Mr. LEWIN remarked that the situation was easier in children—"they tell you when they are ready to get up." If badly concussed they tended to lie quietly in bed.

Post-traumatic Amnesia

Dr. ASTLEY asked about the significance of conflicting statements by the patient on the extent of his amnesia. Sir CHARLES pointed out that there were a number of complicating factors that had to be considered. A post-traumatic amnesia might rapidly shrink over the course of a few hours or days after the accident, and there was the possibility of "islands" of memory being retained within the period of post-traumatic amnesia. He also pointed out that, though almost always there was some retrograde amnesia after concussion, occasionally a patient was encountered with a post-traumatic amnesia of some hours but with a clear memory of the accident. The length of the post-traumatic amnesia was an important factor in assessing the severity of the injury.

Mr. R. P. M. MILES sought guidance on which cases should be referred to specialized head-injuries units and which cases might be managed by general surgeons. Mr. LEWIN replied that in view of their numbers—at a rough estimate at least 150,000 cases of head injury were admitted to hospital annually—it was not possible for a neurologist or neurosurgeon to see every case. There must therefore be some selection. In his experience, approximately 10–15% of cases admitted gave cause for serious anxiety. It was for these cases that facilities for transfer to a unit specially equipped for dealing with head injuries should be available. Sir CHARLES stressed that, as early as possible, a good neuropsychiatric assessment must be made and a firm and competent opinion as to prognosis given. This very materially aided the subsequent rehabilitation of the patient. He also pointed out that, apart from the physical effects of the head injury, the accident might give rise to all sorts of emotional problems which simple psychotherapy might do much to alleviate.

With regard to legal compensation, a question raised by Dr. W. A. OLIVER, it was felt that early settlement of legal questions was probably in the best interests of all concerned. At times, however, the physician felt disinclined to advise an early settlement in view of the possibility of late complications, such as post-traumatic epilepsy. In compensation cases, it would be helpful to be able to specify disabilities that might arise later.

Post-traumatic Epilepsy

On being asked about post-traumatic epilepsy, Mr. LEWIN replied that it was a difficult subject to discuss, as accurate data were not available for civilian injuries. However, reliable information was available for war injuries and of all cases admitted to hospital: in these the overall risk of epilepsy was 3–5%. After simple concussion it was only 1% or less, but in complicated cases, such as those with depressed fractures or symptoms or signs of focal brain injury, the risk rose to 20–25%. A long period of post-traumatic amnesia carried a higher risk. The panel agreed that in most cases the epilepsy developed within 1–2 years. With regard to post-concussional headache, the most important aspect was prevention. With proper rehabilitation the incidence of post-concussional syndromes was very low.

PANEL ON TETANUS

Tetanus proved to be a stimulating and well-attended subject for panel discussion, on Saturday afternoon, under the chairmanship of Dr. J. A. CAMPBELL, of Norwich. The speakers were Dr. L. B. COLE (Cambridge), Dr. D. R. LAURENCE (London), and Dr. H. J. PARISH (Beckenham).

Dr. COLE first discussed the trend of the disease in the past 30 years. He considered that there had been a definite decrease both in the number of cases and in their severity. Although tetanus was not notifiable, this was borne out by the Registrar-General's figures, which had shown 100 deaths annually in the 1930's and fewer than 50 in 1957. In a personal series of 43 consecutive cases seen between 1928 and 1939 he had had a 46% mortality, but in the past nine years the rate was 14.5% in 25 cases. This he considered to be due to factors other than therapy, such as cleanliness in the treatment of wounds and the education of both the public and doctors in giving antitoxin. With regard to a change in the type of wound, in pre-war days cases of fulminating tetanus were seen after severe wounds, but nowadays these would be prevented by A.T.S., which was given automatically. Dr. LAURENCE agreed with this opinion. From his experience in South Africa he had noted that tetanus was commoner in the less severe wounds which would not be brought to hospital and given A.T.S. In answer to a question from the chairman, Dr. COLE agreed that cases were more commonly seen where there was no obvious portal of entry. These might arise from otitis media, following dental extractions, or obstetric manipulations. He had also seen cases in agricultural workers with whitlows, following chronic varicose ulcers, and in dirty children with grazes.

Immunization

Dr. PARISH was then asked his opinion on the best form of immunization, which he said was unquestionably with the use of toxoid. As comparatively few civilians were so treated, A.T.S. had to be given frequently, but it had great disadvantages—namely, anaphylaxis and the fact that precipitins to the serum employed were produced in varying degree, so that with second, third, or fourth doses the duration of protection might be reduced from the expected two weeks to two days. By giving enormous doses of 10,000 units rather than the more usual 1,500 there was only very little increased protection. It must also be remembered that diphtheria antitoxin might predispose to sensitivity.

Active immunization was of proved value in the last world war, and the recommended regime in adults was of three doses with 6–12 weeks between the first two and 6–12 months between the second and third. Dr. Parish stressed that the policy in casualty departments should be the responsibility of a senior surgeon. Patients presenting with wounds should be routinely questioned about previous immunization, and A.T.S. must be given if they were inadequately immunized. If a full course of immunization had been given, 1 ml. of tetanus toxoid intramuscularly was indicated. A routine test dose should be given subcutaneously—not intradermally. Boosting doses of toxoid were advisable at intervals of 5 years and were probably necessary at least twice. Toxoid should not be given until six weeks after A.T.S., as there was too much risk of neutralization with consequent inadequate immunization. But active immunization should be carried out in every case after A.T.S.

Treatment

Dr. LAURENCE then discussed treatment. He said there were three main groups—those who recovered anyway, those who died whatever was done, and a rapidly diminishing group for which the outcome depended on treatment. The recognized regimes were: (1) sedatives, rectal tribromoethanol, intramuscular paraldehyde, or chlorpromazine and barbiturates, or (2) muscle-relaxants with artificial respiration, and the results depended less on the choice of treatment than on the assurance with which it was carried out. It was most important that one person should have full charge of the case and should always be available. This meant he could not be a consultant but should be a registrar or houseman. Treatment should not be switched half-way by altering sedatives. If these were used properly, convulsions were rarely the cause of death. Whether or not relaxants were useful was still controversial in Great Britain; in competent centres their use was probably good. Chlorpromazine was a very effective anticonvulsant. Its effect was on the brain-stem, not on the spinal cord. In large doses it could excite the brain-stem and actually aggravated convulsions. It also produced tachyphylaxis — i.e., a diminishing response to increasing doses. It should be given 4–6-hourly and augmented with barbiturates.

Dr. COLE agreed in the main with these views, but stressed the point that mild early cases did well on sedatives and would recover unless over-treated. He also felt that there was a large group who did well with tracheostomy and sedation, without relaxants. He agreed that fulminating cases rarely recover and for sedation favoured paraldehyde.

Dr. CAMPBELL remarked that it was difficult to decide when to perform tracheostomy. Dr. COLE felt that there were two main factors: one was the severity of the spasms, and the other age—over 60 tracheostomy should be performed early rather than late.

Feeding was then discussed and Dr. LAURENCE stressed that a nasal tube should be passed on admission. This could be augmented with intravenous fluids, but in Durban the latter had not been feasible and an intragastric drip was usually adequate. He stressed the diagnostic point of rigidity of the recti and erector spinae, saying that the patient felt like a "hot statue." He thought that pneumonia was diagnosed more often than it did in fact exist, and this was borne out in a post-mortem series. Penicillin was known to kill the tetanus bacillus and was usually given, but it was of doubtful value in the prevention of pneumonia.

Questions

Dr. A. K. KNOWLES asked whether a large initial intravenous dose of A.T.S. should be given. Dr. PARISH replied that intravenously it was of doubtful value. It was probably of more comfort to the physician, who knew that spores in the wound could produce large quantities of toxin at any time. Intrathecal administration was dangerous and should never be given. Intravenous doses should be given only after a subcutaneous test-dose, followed by an intramuscular test-dose, at intervals of half an hour.

Dr. HOLTBY, of Norfolk, asked which group of adults should be actively immunized. The panel responded firmly that all the population should be immunized. The chairman added that we were all agricultural workers at times.

Mr. M. ELLIS asked the panel's opinion on gastrostomy, which he had found very useful in small children, as it avoided ulceration of the oesophagus. Dr. LAURENCE had used fine polythene tubes and found them satisfactory. Mr. ELLIS also took up the panel on their statement of minor cases that do not become serious by quoting the case of a small boy who had been observed in the ward and discharged home, no A.T.S. having been given, and had returned three weeks later with severe tetanus requiring artificial respiration. It was the policy at Leeds to give toxoid 10 days after A.T.S. for fear of losing a patient from follow-up. Dr. PARISH felt that this was still a gamble, as immunity might not be achieved with this short interval.

PANEL ON THE OBESE CHILD

The chairman at this panel was Dr. J. F. P. QUINTON (Norwich).

The panel opened the discussion with an attempt to define obesity. Professor D. V. HUBBLE (Birmingham) felt that the diagnosis could usually be made just by looking at and weighing the child, though in a strict sense obesity could be defined as a weight 20% or more above the average for the child's height and age. Dr. R. E. SMITH (Rugby) agreed with this definition, and stressed the importance of taking height into account.

The next question concerned the incidence of endocrine causes of obesity in children. The panel agreed that these were extremely rare and could almost be forgotten. Professor HUBBLE had seen only two cases of severe obesity in children due to myxoedema, and no one present had ever seen a true case of Fröhlich's syndrome. Asked by Dr. W. J. L. FRANCIS if there was any place for more precise tests of endocrine function in these cases, Professor HUBBLE replied, No, except in those rare instances where hypothyroidism or adrenal overfunction was suspected. Dr. SMITH cited the basal metabolic rate as being normal in most cases of obesity, though the overall metabolism was probably more important, as shown by the high calorie intake of non-obese athletic boys. In answer to a question whether there was a different incidence of obesity as between boys from private and State schools, Dr. SMITH said that to-day any such differences had largely been levelled out. The panel was not clear whether obesity was more common in girls than in boys, but Professor HUBBLE believed that the prognosis was better in the boys.

Psychological factors in obesity, Professor HUBBLE felt, had been overstressed, though food was undoubtedly a source of comfort to the unhappy, and some mothers might overfeed a child out of remorse for not having wanted him in the first place. Fat people on the whole seemed happy. Was that because they were fat, or were they fat because they were happy? Asked at what stage steps should be taken to correct obesity in children, the panel agreed that the earlier this was done the better.

Treatment of Obesity

Dr. QUINTON asked Professor Hubble to describe how he tackled a case of obesity in a child. Professor HUBBLE explained that he did not favour a weighed diet, but merely urged the mother to reduce the helpings of carbohydrate, and this was usually effective. Having started the regimen it was most important to keep up an interest in the case. One should congratulate the child when this was due and not be too harsh if the results of treatment were poor. On the question of drugs there was some disagreement on whether dexamphetamine should be given. Professor HUBBLE favoured this where necessary, and stressed that children tolerate the drug very well provided it is given only in the morning. Dr. SMITH disagreed with this treatment, and relied more on the children feeling better as soon as they began to lose weight. Dr. A. P. DOUGLAS-JONES said that he had found testosterone to be most effective in curing fat prepubertal boys of 12. Asked if they grew on this treatment, he replied that two of them had attained a height of 6 ft. 3 in. (191 cm.). Professor HUBBLE suspected that this had already been written in their horoscopes and was not the result of treatment.

Dr. IRENE GREEN inquired whether there were any special institutions for the treatment of difficult cases of obesity in children. It appeared that there were none, and several members urged that such an establishment was needed. When necessary, Professor HUBBLE admitted his cases to hospital for a period of intense dieting on a high protein and low calorie intake.

Lastly, the problem of obesity in infancy was raised. Intussusception seemed commoner in fat infants, and these

cases were a poor operative risk. Fat infants usually thinned out when they became mobile, though Professor HUBBLE suspected that the fat infant might often be the forerunner of the obese adult.

TRANSATLANTIC CLINICOPATHOLOGICAL CONFERENCE

A very successful clinicopathological conference on gastroenterological cases was held on Saturday afternoon between panels of distinguished medical men in Philadelphia, U.S.A., and Norwich. They were linked by transatlantic telephone and their voices were transmitted by loudspeaker to audiences in each city. The session was sponsored by Messrs. Smith Kline and French Laboratories Ltd.

The members of the Association's team in Norwich were Dr. W. A. BOURNE (Hove) as moderator, Professor L. J. WITTS (Oxford), Mr. H. C. EDWARDS (London), and Dr. F. H. KEMP (Oxford). Across the Atlantic the Philadelphia County Medical Society's team comprised Dr. H. L. BOCKUS as moderator, Dr. T. E. MACHELLA, Dr. H. J. TUMEN, Dr. C. W. WIRTS, and Dr. A. R. CRANE.

British Problem Case

Professor WITTS opened the proceedings by describing the British problem case.

A widow aged 75 had lived in poor circumstances and on a very inadequate diet for the preceding six years. She had remained in reasonable health until a sudden deterioration occurred one month before admission to hospital with anaemia, weight loss, incontinence, haemoptysis, and the development of an abdominal mass. In the previous year food had tended to stick in the gullet and a severe anorexia had been present. Examination revealed a small, wasted woman, somewhat disorientated and clinically anaemic. Areas of brownish pigmentation were found on her limbs, trunk, and buccal mucosa. Her tongue was somewhat atrophic. The liver was palpable and an apparently separate ovoid mass could be felt in the epigastrium There was evidence of peripheral arteriosclerosis. Laryngoscopy revealed fixity and paresis of the left vocal cord.

Investigation confirmed the presence of anaemia, with a megaloblastic marrow and fresh hydrochloric acid in the stomach. A radiograph of the chest showed an opacity at the base of the right lung, which was shown subsequently to be due to a large hiatal hernia containing stomach, small bowel, and colon. Cavities were apparent in the lateral radiograph of the chest, but it was uncertain whether these were due to abscesses or gas bubbles in the hiatal hernia. Some pneumonitis was present at the right base. Her anaemia showed no response to cyanocobalamin, but a brisk reticulocytosis followed folic-acid therapy. Despite treatment with transfusion and antibiotics her condition steadily deteriorated, with the development of a staphylococcal parotitis, and she died 64 days after admission.

The American panel thought some form of gastro-intestinal carcinoma was present with hepatic and pulmonary metastases. They ascribed the anaemia to multiple causes related to blood loss and malnutrition, and the possibility of a blind loop of bowel trapped in the hernial sac was mentioned by Drs. TUMEN and WIRTS. The hiatal hernia was considered most atypical in that it was on the right side of the abdomen and contained so many viscera. Other diagnoses suggested were jejunal diverticulosis, generalized staphylococcal or monilial infection, amyloidosis, and carcinomatosis from renal or pancreatic primary growths.

Professor WITTS felt the American team had done well in ascribing the anaemia to multiple causes: it was, in fact, due to a blind-loop syndrome, malnutrition, infection, and early hepatic cirrhosis. The presence of the large hernia containing small and large bowel was confirmed, the liver was fatty and showed early cirrhosis, and there was an abscess in the right parotid gland. The totally unexpected finding was that the suspected generalized infection was not of staphylococcal origin but due to miliary tuberculosis.

The American Case

Dr. BOCKUS thought this was a most difficult problem in comparison with the case he had to present to the British team.

An 18-year-old girl had for four years been troubled by daily colicky, abdominal pain felt in epigastrium and lower abdomen, often accompanied by vomiting, often nocturnal, and quite unrelated to meals. A year before admission her pains became more frequent and severe, and alternating constipation and diarrhoea developed. A loss of 15 lb. (6.8 kg.) had occurred in this period. Her stools did not appear fatty and had not contained blood. There had been amenorrhoea for a year before admission. The patient had had urticarial reactions to penicillin and sulphonamides in the past, but had previously been well.

Examination was negative beyond revealing anaemia and moderate abdominal tenderness. Investigation showed evidence of an iron-deficient anaemia, a raised sedimentation rate, and slight hypoalbuminaemia, and a mild transient leucocytosis had developed a week after admission. Examination of the stools showed the presence of occult blood. Radiological investigation was said to have shown a duodenal ulcer. Absorption of vitamin B_{12} was defective (Schilling test). While in hospital, evidence of gastric retention was obtained on two occasions by the finding of excess of fasting gastric contents. For these reasons a laparotomy was advised.

The British team expressed an emphatic unanimity of opinion in ascribing the patient's symptoms to a granulomatous regional enteritis involving duodenum and ileum and inducing partial intestinal obstruction, blood loss, and malabsorption. They doubted if a peptic duodenal ulcer was present in addition, ascribing the radiological changes to duodenal involvement by the granuloma. Tuberculosis, polyposis, small intestinal tumours, Hodgkin's disease, collagen disease, carcinoid syndrome, and Meckel's diverticulum were considered but dismissed as unlikely. Dr. KEMP in a masterly review of the radiological changes thought they would be compatible with an enteritis involving duodenum and distal ileum.

Dr. BOCKUS, in Philadelphia, then revealed the predicted diagnosis to be entirely correct, in that at laparotomy a typical Crohn-type lesion was found to involve duodenum and terminal ileum, associated with hose-pipe thickening of the bowel wall and enlargement of the regional lymph nodes. The lesion was treated by two short-circuiting procedures, and the patient had gained weight rapidly after the operation. He congratulated the British team in so competently dealing with their problem, and stressed the frequency of amenorrhoea in young women as a presenting symptom of Crohn's disease.

SOCIAL OCCASIONS

The Civic Reception on the first evening of the Meeting was described last week (*Journal*, October 31, p. 878). Another notable reception was that given on Friday evening at Samson and Hercules House by the chairman (Mr. J. M. RIDLEY THOMAS) and members of the Norwich Division of the B.M.A. Here in a delightfully informal atmosphere old friends met again and new acquaintances were made. The hospitality of our Norwich hosts could not have been surpassed. On Saturday, after the transatlantic conference, Messrs. May and Baker Ltd. were the hosts at a well-attended cocktail party at the Assembly House. In the evening there was the choice of seeing Goldoni's "The Servant of Two Masters" at the Maddermarket Theatre or attending a recital for two pianos, at which Cyril Smith and Phyllis Sellick performed, at the St. Andrew's Hall. The concert was arranged by the Norwich Philharmonic Society.

On Sunday after Matins the Dean led a tour round the Cathedral, and there was also an exhibition of the city regalia in the City Hall, attended by the Lord Mayor. During the Meeting, B.M.A. members were received as honorary members of the Strangers' Club and the Royal Norfolk and Suffolk Yacht Club.

Nova et Vetera

BIRTH OF A HOSPITAL

A reception at the National Hospital, Queen Square, last Monday commemorated the public meeting on November 2, 1859, at which it was decided to found the hospital. This meeting was held in the Egyptian Hall of the Mansion House, under the chairmanship of the then Lord Mayor of London, Alderman D. W. Wire. "Feeling a deep interest in the sufferings caused by Paralysis and Epilepsy," wrote Alderman Wire in his invitation to the wealthy and benevolent, "I have summoned a Public Meeting . . . for the purpose of Establishing an Institution for the Relief of persons so affected." So successful was this meeting that in 1860 the National Hospital for the Paralysed and Epileptic was founded at 24, Queen Square.

The impetus for this momentous event came from two Victorian spinsters, Johanna and Louisa Chandler (in the illustration Johanna, the elder, is standing). Helped by their brother, Edward Chandler, they enlisted the support of Viscount Raynham for their proposed institution, and the Mansion House meeting was then arranged. How the two sisters reached their decision to found a hospital for the paralysed and epileptic is best told in the words of an early advertisement for the hospital's pension fund:

"Saddened by the suffering of one so dear, and deeply impressed with the conviction that, if those surrounded with all the comforts of life thus suffered, the condition of the Paralysed Poor must be pitiable indeed, the sisters conceived the idea of founding a Charity for the special benefit of persons so afflicted; but they were not rich; they knew, too, that the wealthy and benevolent were besieged with applications, and rightly judged that theirs would be cast aside. 'We know a little art,' said the elder sister, 'we will practise it until we have gained £200; we will offer that in earnest of our sincerity, and God will incline some kind heart to take up the cause.' So the little fund was worked for, gained and offered; devoted men and women *were* found to take up the cause, and the Hospital for the Paralysed and Epileptic was established; but the younger sister (always delicate) lived only to see the commencement of the good work; with her dying breath she blessed it, prayed for its success, and entered unto her rest."

The "little art" the sisters knew was the decoration of drawing-room bric-à-brac with cowrie shells. From such small beginnings sprang the premier hospital in the Commonwealth for the study and treatment of nervous disorders.

[From a photograph of a painting destroyed in the war.]

New Appliances

AN UMBILICAL CORD CLAMP

Mr. D. J. MACRAE, consultant obstetrician, writes: The clamp shown in Fig. 1 has right-angled serrated jaws with a parallel action which permits compression of the cord equally over its whole area and has the advantage of containing a large cord within its grip (Fig. 2, A). Ordinary

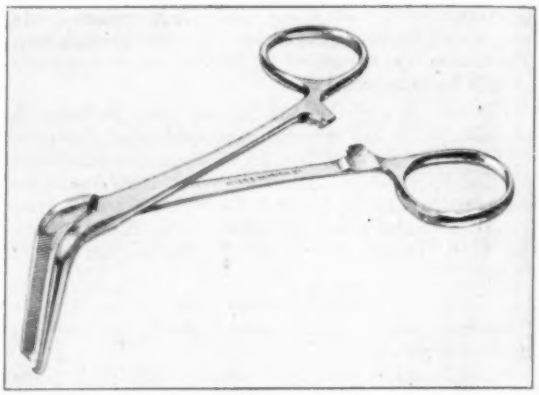

FIG. 1

straight forceps lack these features and are sometimes dangerous, as the end of the jaws may lose their power when the cord is thick and allow leakage of blood (see Fig. 2, B). The clamp is light, to prevent it pulling on the cord when it is left on for some time, and its screw-joint makes it easy to clean.

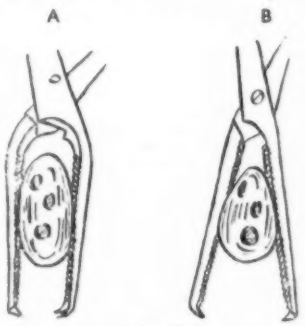

FIG. 2

The clamp is safe when used on its own, as in forceps or caesarean deliveries. Since haemorrhage is not uncommon, however, from a slack ligature, or following shrinkage of the cord, routine use of the cord clamp along with a ligature is recommended. A safe practice is as follows: When the cord has stopped pulsating it is tied with two ligatures of twisted thread and divided between the ligatures; the clamp is then placed on the cord about one inch (2.5 cm.) away from the umbilicus. When the baby is bathed a short time afterwards the clamp is replaced by a ligature and the cord trimmed close to this. The tying of the final ligature on the crushed area completely occludes the vessels and allows the formation of a knot which does not slip.

The forceps were made for me by Allen & Hanburys, Ltd.

Most recent statistics place Australia's population at 10,061,000. This is an increase of 215,000 during the 12 months up to the end of June. Natural increase accounted for 138,000 and migration for 77,000. The increase was 12,000 more than in the previous year. In June Australia had 106,000 more males than females. (*Radio Australia News.*)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Consciousness during Surgical Operations

SIR,—In the course of the excellent leader on consciousness during surgical operations (*Journal*, October 24, p. 810) it is stated that "controlled respiration with hyperventilation of the lungs, a universal adjuvant to the relaxants, added its own quota of analgesia."

I would venture to suggest that continued hyperventilation with its attendant alkalosis and shift of the haemoglobin-dissociation curve to the left, with hypotension and vasoconstriction, is by no means innocuous. Many anaesthetists believe that it is desirable to maintain the carbon-dioxide and *p*H levels as near to their normal values as possible. After all, the hyperventilation syndrome in conscious patients is now regarded seriously by physicians: why should we produce it intentionally in the unconscious?—I am, etc.,

St. Bartholomew's Hospital, London, E.C.1. C. LANGTON HEWER.

SIR,—Following your leading article (*Journal*, October 24, p. 810) on consciousness during surgical operations, the daily press[1] has suggested that modern advances in anaesthesia may lead to patients being aware of pain during surgical procedures, and by implication lay the blame on the use of relaxants. This publicity is to be deplored, and is likely to shake the patient's faith in anaesthesia. Your leading article was based on Graff and Phillips' report[2] of a patient who remembered the insertion of the airway and had other unpleasant sensations during anaesthesia with thiopentone, nitrous oxide, oxygen, suxamethonium, and intravenous lignocaine. Spontaneous respiration was present throughout, although it was claimed that the ventilation was assisted. An endotracheal tube was not passed. It would seem to us practically impossible to assist the respiration adequately when a mask and airway only are used, especially if the patient, as in this case, is in the lithotomy position. We have evidence of the low *p*H and high pCO_2 values which can exist under more favourable circumstances when it is alleged that respiration is being "assisted." We believe that such hypoventilation tends to "arouse patients," and it does not surprise us that under the conditions described difficulty was experienced in keeping this patient asleep.

For 11 years or more one of us (T. C. G.) has emphasized the importance of complete control of the respiration when relaxants are used. Our experience has taught us that it is virtually impossible to assist respiration successfully without assuming full control. Seven years ago attention was drawn to the part played by this control of the respiration in maintaining unconsciousness.[3,4] Our subsequent work has amply confirmed this and suggested a possible mechanism.[5] In all our experience with the use of the nitrous oxide–oxygen-relaxant technique with controlled respiration we have never come across any patient with a memory of the operation. Those instances which have been reported have always been attributable to a technical error or misjudgment, such as the nitrous-oxide cylinder becoming exhausted.[6] Technical errors of misjudgment can have unfortunate consequences no matter what form of anaesthesia is used.

The use of non-toxic anaesthesia has proved one of the greatest advances in poor-risk patients and cardiac surgery. Obviously all will endorse your statement that "the patient's need to be unconscious of his surroundings and free of pain is paramount," but it would be disastrous if your leading article led to an impression that this was certainly achievable only by the depressant anaesthetics ether, trichloroethylene, and halothane. One would respectfully request that writers of leading articles might beware of the possibility of sensational reports appearing in the daily press and of the subsequent effect on our patients.—We are, etc.,

CECIL GRAY.
IAN C. GEDDES.
Department of Anaesthesia, University of Liverpool.

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4 Dundee, J. W., ibid., 1952, **2**, 893.
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SIR,—In your leading article "Consciousness during Surgical Operations" (*Journal*, October 24, p. 810) you state that there is clearly a need for some means of detecting the presence of consciousness in an unresponsive curarized patient.

For some years I have anaesthetized patients undergoing laminectomy with an initial dose of thiopentone and maintained anaesthesia with 75% nitrous oxide and 25% oxygen. Relaxation to the point of apnoea has been obtained with an intravenous infusion of 0.1% succinylcholine chloride. An early sign of the return of consciousness both during and at the end of anaesthesia has been an "alertness" of the eye, dilatation of the pupil, suffusion of the conjunctivae, and lacrimation. These signs are an indication for the need to administer an adjuvant drug. Using these eye signs as a guide, I have never had a patient complain of regaining consciousness during an operation.

I would suggest that clinical observation on the part of the anaesthetist is more valuable than expensive and heavy equipment, for most of the anaesthetist's working days are spent in situations where such equipment is not available.—I am, etc.,

London, W.1. JOHN GORDON.

Primigravidae in Rented Rooms

SIR,—Owing to shortage of maternity beds, it appears that a very unsatisfactory routine may become established, at least in this part of London. Young married women, living in rented rooms, are unable to book a hospital bed for a first confinement except on medical grounds. The district midwives do not book them, owing to their unsuitable home conditions. They are referred to a general-practitioner obstetrician, who must ask the Emergency Bed Service to accept a normal first delivery as an emergency on social grounds.

These mothers, often under 21 years and away from the support of parents, are left in an anxious state, not knowing where they will have their first baby, and without any positive assurance that a bed will be found at all. They are often worried about being given notice from rented accommodation if they should be unfortunate enough to be delivered at home. I feel this situation is most unsatisfactory to the patient and doctor.—I am, etc.,

London, S.W.12. JOHN C. DARNLEY.

Earliest Symptoms of Measles

SIR,—Your annotation on the earliest symptoms of measles (*Journal*, October 10, p. 687) is of great interest to us general practitioners and prompts me to record an unusual case. Although Goodall[1] drew attention to the illness of infection 34 years ago, little heed has seemingly been given to it since, probably because it is likely to be observed by the general practitioner, who has been disinclined to publish interesting observations made in his practice.

During a measles epidemic in this district, a boy aged 3 took ill three days after his elder sister had developed a typical measles rash. He commenced to shiver, and several hours afterwards vomiting occurred. He continued to vomit frequently during the next 24 hours, at which time I was called in. The boy had a temperature of 102° F. (38.9° C.), was lethargic, and had mild neck rigidity and a positive Kernig's sign. No other signs were present (urine examination was negative).

I observed him carefully during the next 36 hours. Fever and frequent vomiting continued and signs of meningeal irritation increased. I arranged for a domiciliary consultation with a paediatrician, who confirmed the presence of marked meningismus. He found no other physical signs and suggested that if the boy did not improve within 24 hours he would admit him for a diagnostic lumbar puncture. Five days after the onset of his illness vomiting ceased and temperature returned to normal.

The boy remained lethargic, resented being sat up for examination, and refused all solid food, although he accepted fluids. At this stage the paediatrician drew my attention to the article[2] mentioned in your annotation. This was reassuring. Two weeks after the onset the boy improved but still showed no inclination to get up and walk about. Then on the 18th day he developed catarrhal symptoms followed by a cough. Koplik's spots were observed on the 19th day and a typical measles eruption appeared 21 days after he had taken ill (24 days after his sister's rash had appeared). Apart from the elder sister he had no other known contact with measles.

This child therefore seems to have had a diphasic measles illness with a very prolonged first phase which included meningismus. The possibility of the first phase being due to a virus other than that of measles cannot be, of course, definitely excluded.—I am, etc.,

Smethwick, Staffs. H. MACLEAN.

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Tongue-tie

SIR,—Tongue-tie, like phimosis, is a rare but definite and important congenital deformity. Just as one meets among Army recruits some who have never in their lives had the foreskin back, so certain children are handicapped, occasionally very seriously, by being unable to get the tip of the tongue against the hard palate. In infants (Fig. 1) the effects are an inability to compress the natural or artificial teat, with a consequent slowing of feeding that at the best is exasperating and at the worst produces starvation. One of my cases had the family history that the father had been wasting away as a small baby till an aged midwife produced a scissors from her pocket and cut the frenum there and then, with the result that he put on a pound in the next few days.

In older children the effect is a curious muffled voice that can be imitated by trying to talk with the tip of the tongue held under the lower teeth (Fig. 2). The improvement in articulation in this child after freeing the tongue was immediate and very marked. A transverse incision through the mucosa exposed a band of fibrous tissue rather like that of the chordee of a hypospadias. When this was divided the incision was with ease extended longitudinally to four centimetres in length, and sutured by a few catgut stitches.

Of course the snipping of tongues and uvulae as a routine was grossly overdone at one time (is the latter operation ever done now as a cure for cough?). But anyone who has heard the comments of a mother who, after being assured at several clinics that she is fussing

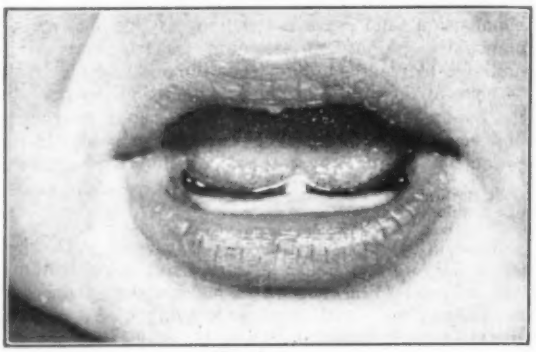

FIG. 1

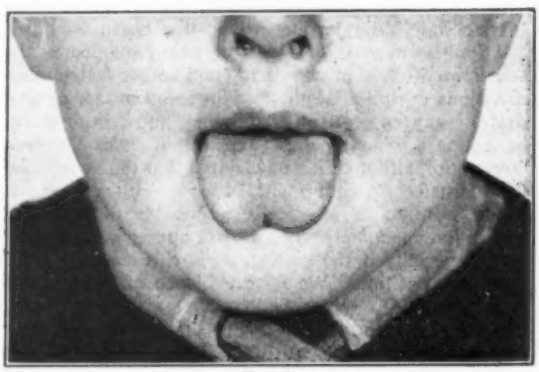

FIG. 2

about nothing, has finally had her troubles settled, is unlikely to agree to the "universal negative" so frequently heard on the subject. Incidentally, as in surgical attacks on the tonsils, the adenoids, and the prostate, the danger of bleeding is from veins, not arteries.—I am, etc.,

London, W.1. DENIS BROWNE.

Service Psychiatrists

SIR,—As an infantry battalion R.M.O. during the North-west Europe Campaign 1944–5, I should like to do something to restore some kind of perspective. Serving psychiatrists were not all as bad as are painted in the letters of Mr. Michael Harmer (*Journal*, October 10, p. 696) or Dr. Richard G. M. Keeling (*Journal*, October 24, p. 823). I found the psychiatrists I had to deal with sensible and practical in their approach and not without fighting experience; one indeed had been in the Sicily air drop.

I did find that casualties I had to evacuate with battle exhaustion were by no means all cowards; indeed, it is only a fool, and a dangerous one at that, who is not frightened in battle. Two of my psychiatric casualties had previously won immediate awards for gallantry in the field. I found on several occasions casualties of mine who had been broken by the strain of continued battle were returned very shortly afterwards from field dressing stations quite useless for any further action and needing evacuation immediately. In fact, I learned to put a request for a psychiatric opinion before "Return to Unit" on the field medical card in such cases.

I suspect that much of the criticism of Service psychiatrists dates from the first half of the war when some psychiatrists were let loose with inadequate understanding of the problems of military medicine and psychiatry. As training methods and selection improved, the standard of psychiatric service provided became very high, and I personally, as an R.M.O., had good reason to be grateful for it.

As regards Dr. Keeling's stretcher-bearer on a charge of cowardice, I too came across one or two cases of this kind. I did find in most instances that the man's comrades were well aware that he was about to crack; the fact that he was subsequently dealt with in a humane manner, and that the punishment was mitigated in accordance with a psychiatrist's recommendations, did not affect morale. Indeed, many of the battle-weary cases who might subsequently have run away in the face of fire were referred to me for evacuation by their own officers, who realized their unfitness to carry on. I am sure that in the second half at least of the war psychiatrists did much more good than harm. That they dropped clinical bricks occasionally I do not doubt; however, I saw some pretty curious bricks dropped in the field of general medicine and surgery as well from time to time.—I am, etc.,

Netherne Hospital, Coulsdon. H. E. S. MARSHALL.

SIR,—Apparently the season for baiting the "trick-cyclists" is again in full spate. In the lay press this pastime is never out of season, but it is not often that Army psychiatrists are honoured by so much attention as at present in the *British Medical Journal*.

As doctors we are precluded from foolish self-advertisement, but this does not prevent either the laity or other medical men giving us the publicity that fills our consulting-rooms. Whether this publicity is favourable or the reverse does not seem to matter. Firms who advertise on I.T.V. know that, provided they buy time and space on the screen, they will sell their products and it really does not matter how banal or fatuous the actual advertisements are. Mr. Michael Harmer's original grievance (*Journal*, October 10, p. 696) against you, Sir, was that you allotted so much space to Professor Crew's review of Dr. Ahrenfeldt's book. In this he seems to have been fully aware of the advantage that would accrue to us from so many columns of publicity in the *British Medical Journal*. However, his protest to you has not only given us a further column of unsolicited publicity in the *Journal* but also has set an example for other correspondents to follow suit. Although I have been familiar with Ahrenfeldt's work for some time, I was on holiday on September 26 and would have missed this excellent review were it not for Mr. Harmer's timely letter. I am grateful to him.

As for the case of a sergeant who stood to attention while a V.1 was exploding in the vicinity, in February, 1945, I was conducting a medical board on a private soldier in the neighbourhood of Antwerp, then under constant fire from V.1's. There was a cut-out overhead and the medical board, quite rightly, took cover under my table. After the explosion our private soldier was still standing to attention and we decided he was so depressed and apathetic that he was incapable of preserving himself from common dangers. He was psychotic. It is no military virtue to expose oneself unnecessarily to the effects of enemy action, especially when the enemy is miles away. A soldier's duty is to take avoiding action, so as to prevent himself becoming an unnecessary casualty and a drag on the military machine in a theatre of war.

Many of us who had had ample pre-war military experience and training would much have preferred to do some "real soldiering" during the war, but our first military duty was to do what we were told without "belly-aching" and that was to carry on with our civilian specialty in a military setting. We had often to console ourselves with the knowledge that "they also serve who only stand and 'trick-cycle.'" Now the incontrovertible facts of history (fully documented by Ahrenfeldt) show that our efforts were not altogether unavailing, and, however many our mistakes (from which I hope we learned something), we can rest content with the praise of men like Sir Ronald Adam, Sir Alexander Hood, Wavell, Auchinleck, Eisenhower, and the comprehensive review of Professor F. A. E. Crew.—I am, etc.,

Manchester, 2. J. F. WILDE.

SIR,—Mr. Michael Harmer's letter (*Journal*, October 10, p. 696) sets out a problem with which all general-duty officers are faced in time of war—namely, the direct recruitment of civilian specialists into the armed Forces without the benefit of combat experience as a junior medical officer. We have all suffered from so-called specialist officers who would not know the stern of H.M.S. *Victory* from Marilyn Monroe. A year in a small ship is a remarkably enlightening experience.—I am, etc.,

Health Department, Brighton, 1. W. S. PARKER.

SIR,—Your correspondence has produced a good deal of adverse criticism of the Service psychiatrist (*Journal*, October 10, p. 696; October 24, p. 823), and many of us who were in the Services during the late war share these feelings. Is it really fair, however, to place all the blame on the psychiatrists? So far as the Army is concerned I would place most of the blame on the War Office (the D.G.M.S. in particular); and then on the rest of us (in descending order of culpability according to rank) for meekly failing to give voice to our real opinions.

With six years' war experience as officer-in-charge of medical divisions or acting O.C. of military hospitals, I frequently played some part in the invaliding out of soldiers on psychiatric grounds. Private A is repeatedly reporting sick for symptoms with no organic basis and his unit M.O. is clearly of opinion that he is in fact "swinging the lead." The O.C. sends for the M.O. and intimates that Private A is more a liability than an asset and he must either cure him, get rid of him, or put him on a charge for malingering. The M.O. sends him to see a medical specialist, who, after various investigations, comes to the same conclusion as the unit M.O. but "passes the buck" to the psychiatrist. He, probably

confronted with more cases than he can possibly examine satisfactorily, takes the line of least resistance and labels him "anxiety neurosis," "psychopathic personality," or "temperamental instability," and advises invaliding. The psychiatrist is blamed for enabling to "get his ticket" a man who should have been disciplined—but all of us who held senior rank must share in the responsibility for this abuse of the term "invaliding."

Finally I should like to protest against the insinuation in some of your correspondents' letters that psychiatrists were greater cowards than the rest of us under fire.—I am, etc.,

Reigate, Surrey. T. W. PRESTON.

SIR,—It would seem, on the authority of Mr. Michael Harmer (*Journal*, October 10, p. 696) and Dr. Richard G. M. Keeling (*Journal*, October 24, p. 823), that psychiatrists must have sadly deteriorated since my time in the 1914–18 war. This might naturally be expected to arouse a sense of gratification in my all-too-human heart were it not for the fact of the all-too-familiar ring about these same old crusted criticisms.

Dr. Keeling is even more damning than Mr. Harmer. His thrilling anecdote of the brave C.O. of the field ambulance in Tunisia taking the two pusillanimous psychiatrists to see the regimental posts is enough to disgrace the whole tribe. It was silly of them to ask to be shown a battalion position when their intellectual equipment, for which they are renowned, should have indicated the advisability of using field glasses. About the man who left the stretcher squad and ran rapidly in the direction of Algiers, I hope Dr. Keeling was not too disappointed when the psychiatrist was successful in reducing the charge of cowardice in the face of the enemy to absence without leave. Or did he think the man should have been shot out of hand without benefit of psychiatry? He does not say whether the man ran fast enough to reach Algiers. Incidentally, Dr. Keeling's fierce brigadier is irrelevant and nowadays largely a stage figure of fun. After all, his fierceness is only a defence reaction.

As for the comic minute of Mr. Churchill, quoted by Mr. Harmer, in which the psychiatrists are eloquently equated with hangers-on and camp followers, the profound conclusion, I suggest, is forced upon us that a sense of the ridiculous need not be combined with greatness. Should a further demonstration of this be required let me refer Mr. Harmer to the recent account in a Sunday paper of some similarly entertaining remarks alleged to have been made by the same Prime Minister about our own Lord Moran. In my opinion they were somewhat exaggerated.—I am, etc.,

Hythe, Kent. FREDERICK DILLON.

SIR,—I should like to make a few comments on the letter written by Mr. Michael Harmer (*Journal*, October 10, p. 696). Mr. Harmer appears to be critical of the R.A.F. psychiatrist who gave a lecture on "Flying Stress" because he (the psychiatrist) had never been on an operational station. Although the appropriate R.A.F. authority would doubtless have been well advised to have arranged for the lecture to be given by an officer with *first-hand* knowledge of his subject, one is at a loss to understand the "embarrassment" by which the lecturer's audience was afflicted on hearing the speaker confess that he had no practical experience of flying. It was probably not beyond the compass of the lecturer to make some useful observations on "flying stress" without himself having experienced the phenomenon, or been personally exposed to conditions apt to produce it. For instance, one cannot conceive of an assembly of troops having their confidence sapped by a suspicion that the medical officer delivering a lecture on scabies or venereal disease had never himself contracted these particular ailments.

The behaviour of the Army sergeant in standing stiffly to attention during the critical moments of a V.1 attack can only be described as an act of singular inanity, and no doubt the diagnosis was hurriedly changed from "lack of moral fibre" to "lack of cortical neurones." The Army authorities did not encourage personnel to expose themselves to *needless* risk. One marvels at the ubiquitous nature of your correspondent's wartime activities if in truth the anecdotes at his command stem from personal observations and not from idle hearsay in the officers' mess.—I am, etc.,

Menston, Ilkley. J. TODD.

SIR,—I hope that psychiatrists will not fall to the bait recently dangled in your columns by Mr. Michael Harmer (*Journal*, October 10, p. 696). There is so much work to be done at present in psychiatry that we have neither time nor energy to waste in discussing things which are long past.—I am, etc.,

Driffield, East Yorkshire. J. NEWCOMBE.

Fees for Drug Trials

SIR,—I understand that there is an obligation on Members of Parliament to "declare their interest" in any subject before they speak in debate, and that local councillors are forbidden to vote on matters in which they have a financial interest. I am accordingly amazed to discover that over the past few years some doctors who have published papers on trials of new products are in the habit of receiving fees, in money or kind, for doing so.

In my opinion an injustice is done to all articles dealing with this aspect of medicine, for many other people, apart from myself, will immediately regard them as tainted and suspect, however sincere and unbiased the authors may be.

I feel that it should be the policy of the editors of medical journals to insist that if any payment or grant is received by the author of any paper submitted to them, this information should be revealed in the various acknowledgments made.—I am, etc.,

London, N.W.11. E. CRONIN.

Press Publicity

SIR,—I imagine many readers of the *Journal* must have been disturbed and surprised to read the account of the Norwich Clinical Meeting carried by the *Daily Telegraph* of October 24. In the light of the circular we all recently received from Association Headquarters about the undesirability of publicity, it was bad enough that the surgeon and anaesthetist concerned in the caesarean section which was televised over a closed circuit should have been named in the public press. That the patient and her family should have been similarly identified was even worse.

The article read as though its writer, John Prince, had been briefed by someone present in the audience, and many laymen must have been left with the impression that it was based on an official "hand-out" from an Association spokesman. That there are many of us who would not be surprised to learn that this last was indeed the case should serve to remind Council that its avowed policy of keeping the lay press happy is viewed with deep concern by a large body of opinion within the Association. It is as a result of this same policy that we so often read in Friday morning's newspaper a version of an original article in the *Journal* which we cannot read until the next day.

Is the dignity and prestige of our profession really being helped by so assiduously courting the favour of the popular press? Is not a public relations officer proving to be both a useless luxury and evidence of a wrong approach to the maintenance of our profession's reputation? Is it not time that Council had second thoughts about this whole matter of public relations?—I am, etc.,

Loughton, Essex. DONALD V. BATEMAN.

*** There was no official "hand-out." Representatives of the Press were excluded from the television demonstration and heard of the caesarean section by chance and not by anyone's design.—ED., *B.M.J.*

The Norwich Meeting

SIR,—May I be allowed to add my own thanks to your own well-merited appreciation (*Journal*, October 31, p. 872) of the excellence of the arrangements made for us at the recent Clinical Meeting at Norwich?

The historical beauty of the city and the generous co-operation of the civic and the ecclesiastical authorities made Norwich an ideal venue for such a meeting. The subjects of the lectures and symposia were well chosen, and the eminent consultants who came to conduct and to speak in these gatherings added distinction to the proceedings. But the success of the provincial clinical meeting and the continuation of the series, so satisfactorily started at Southampton last year, must depend in the end upon the calibre of the work shown by the local doctors. It is here that Norwich is to be particularly congratulated. Both in the clinical demonstrations and in the television programmes they showed that their clinicians were abreast of, and adding their quota to, modern advances in knowledge and in techniques.

The demonstrations staged in series through the Friday afternoon were brief yet unhurried, lucid without being condescendingly simplified, and, Sir, to use your phrase, both informed and informative. The television programmes were shown in a theatre, whose comfortable raked seating allowed everyone present a good view of the screen. They were held at times when they were in competition with no other part of the programme, and this materially reduced the distractions so often caused by the comings and goings of members endeavouring to see part of the television programme between fulfilling other commitments. The organization and timing of both the demonstrations and the television were first-class. Much careful thought and hard work must have gone to their preparation.

Our thanks are due to all who took such pains to arrange for us so memorable a meeting, one that will set a very high standard for emulation for the organizers of clinical meetings of future years.—I am, etc.,

Bromley, Kent. A. TALBOT ROGERS.

SIR,—As a member of the B.M.A. who has attended a number of B.M.A. meetings in Britain, the joint Annual Meeting of the B.M.A. with the Canadian B.M.A. at Toronto, and a number of other interesting medical congresses, I would like to express my appreciation of the efficiency with which the meeting at Norwich was organized.

Those who were fortunate enough to attend the clinical sessions of the congress at Norwich must have been impressed by the great care which was taken by the organizers in presenting the demonstrations and making it easy for visitors to hear so many sessions in the two days available. The colour-television demonstration of operations carried out by surgeons in the Norfolk and Norwich Hospital and transmitted to the screen in the Theatre Royal must have impressed everyone and shown the importance of this new field of education in future medical education. Much credit must be given to Messrs. Smith Kline and French for the arrangement of these valuable television presentations. The final transatlantic clinical conference on gastro-enterological cases arranged in connexion with the Philadelphia County Medical Society and leading physicians in Britain was remarkably instructive and well carried out. Such demonstrations will make it possible in future for medical practitioners in this country to attend important congresses overseas without going to the expense of travelling overseas for the purpose.

Finally, the arrangements for hospitality to visitors to the congress were most efficient, and all who attended owe a great deal of gratitude to those who took such particular care in the arrangements of a most successful clinical meeting.—I am, etc.,

Cambridge. RALPH A. NOBLE.

German Medicine Abroad

SIR,—The problem raised by Professor W. C. W. Nixon (*Journal*, October 10, p. 693) is very serious, and unfortunately the decline of the prestige of British medicine abroad is too apparent. The remedy does not consist in ending British Physicians and surgeons lecturing abroad, because in my experience such lecturers—if one expects certain outstanding personalities—are not useful, unless they are invited by the universities of these countries.

The remedy, in my opinion, consists in encouraging foreign doctors to come to England and see British work, instead of discouraging them with formalities and red tape, as has unfortunately been done up to now. Foreign doctors wishing to study the work of British medicine have to fill up, before they come to England, the form sent by the British Postgraduate Medical Federation. In this they have to state their family background, to demonstrate their solvency, their sponsorship by the British Council, and they must name persons who will vouch for them during their stay in England. Compare this with what happens in France, Germany, and Switzerland where foreign graduates come without any formality, are received with open arms by the universities, where they state their requirements and are sent immediately to the appropriate institutions. Their names even appear in medical journals as arriving for postgradute studies. Can you blame foreign graduates if they prefer the easiest way? Miss G. M. Sandes (*Journal*, October 24, p. 822) states that in Greece the postgraduate experience in Paris is considered to have immense prestige value. I can assure

her that in the two or three years after the end of the war, thanks to the work of a few Greek pupils of mine, London was considered as conferring higher prestige. This, however, unfortunately, has not been maintained.

I see only one practical solution, the enlargement of the principle of the Fellowship of Postgraduate Medicine's work. Foreign doctors should be received in England, without any formality, in an office connected with the university, where they would state their requirements and would be sent directly to the proper institutions. We have first-rate teachers who meet with great courtesy the foreign graduates who manage to reach them, and those who have reached them return to their own country with great admiration for British medicine. Why not cut the red tape, thanks to which only a small minority of foreign doctors manage to see the work of our splendid clinics and laboratories? The solution I propose does not need money, but understanding.—I am, etc.,

London, W.1. A. P. CAWADIAS.

Dietary Fat and Serum Cholesterol

SIR,—In a recent paper Keys *et al.*[1] have reported that the administration of arachidonic acid concentrates to human subjects resulted in an elevation of serum cholesterol. The explanation suggested by these authors for this phenomenon is that, when excess of arachidonic acid is administered, linoleic acid was being spared for the synthesis of lipoproteins. In this connexion the following observations arising from some of our recent investigations may be of some interest.

In the course of an experiment designed to study the effects of different dietary fats on the serum cholesterol levels in monkeys (*Macacus radiata*) we had maintained two groups of monkeys on diets supplying 25% of fat as nigerseed oil (linoleic acid content 70%). One of these groups was rendered pyridoxine-deficient by total withdrawal of pyridoxine from the vitamin mixture and by the addition of 3 mg. of desoxypyridoxine daily to the diet. Our object in carrying out this experiment was to investigate if the blocking of the conversion of linoleic acid to arachidonic acid by the withdrawal of pyridoxine would, in any manner, modify the effect of nigerseed oil on the serum cholesterol levels. The animals of the pyridoxine-deficient group had a vitamin-B_6 activity equivalent to 3 γ/100 ml. serum, which corresponds to the levels reported by Greenberg and Rinehart in their experiments.[2] The animals of the control group had about 9 γ/100 ml. serum. Serial cholesterol estimations showed that in the control group there was a gradual fall in the serum cholesterol concentration. The mean deviations from the basal level for serum cholesterol in the control group on the 10th, 20th, 30th, and 40th days were −14, −14, −10, and −42 mg./100 ml. serum, while in the pyridoxine-deficient group the mean deviations from basal level on the corresponding days were +8, +23, −2, and −12 mg./100 ml. serum. There was thus a rise in the serum cholesterol level in the pyridoxine-deficient group in the first few days, but this was followed by a fall thereafter.

The rise in serum cholesterol in the pyridoxine-deficient group in the first few weeks is consistent with the suggestion of Keys *et al.* that, when the conversion of linoleic acid to arachidonic acid is blocked and linoleic acid thus deviated for other functions, a rise in serum cholesterol may be expected. When we observed a rise in serum cholesterol in the pyridoxine-deficient group in the initial stages, we considered the possibility that the conversion of linoleic to arachidonic acid was essential to bring about the depression of serum cholesterol. The finding of Keys *et al.* that administration of arachidonic acid actually elevated serum cholesterol would appear to run contrary to this possibility.

The explanation for the fall in serum cholesterol in the pyridoxine-deficient group in the later stages is, however, not clear. It is of course possible that the deprivation of pyridoxine in our experiment was not severe enough to entirely block the conversion of linoleic to arachidonic acid. Incidentally, it will be seen that in the subjects of Keys *et al.*, after the withdrawal of arachidonic acid, the rise in cholesterol levels persisted for a few days and was later followed by an appreciable fall of serum cholesterol concentration below the basal level. The significance of this finding has also to be elucidated. Our observations are, however, of a preliminary nature, and we expect that further experiments which are now in progress will help to confirm these findings.—We are, etc.,

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Reversible Mutations

SIR,—Pessimism has seldom produced any great advance in human achievement, and to adopt the view about cancer suggested by Sir Macfarlane Burnet (*Journal*, October 17, p. 720) would be to abandon almost all attacks upon the problem of malignancy or to maintain only some partial approach without any real belief that the problem can be solved. With his suggestion that somatic mutation is the basic cause of cancer many will agree, but to go on "that mutations are irreversible and there is no presently conceivable way in which the process can be prevented" is neither in keeping with our present knowledge of the subject nor a stimulation to anything but what he described as curative approaches which "must be indirect and largely empirical." Surely the literature is full of instances where a neoplastic process, even in such an invariably fatal condition as leukaemia, has been reversed either by some deliberate interference with the process or even in what appears to be a completely spontaneous way.

But even if there were not those instances, we are reaching a point in our examination of the intracellular mechanism of the cancer cell where we can say that it is a cell distinctly different from all others in the human body. It is quite clear that the variation in the function of the different groups of cells in a complex animal body must be based on chemical differences. Neoplastic cells differ in various ways from the normal cells among which they arise. Although the picture is still incomplete, it is possible to write down, from our present knowledge of intracellular metabolism, a plausible mechanism for neoplasia wherever it occurs. The changes in cellular metabolism which this implies may be molecular or even intramolecular and dependent upon changes in electron balance. There is nothing in this to suggest that the process will always be irreversible and much to suggest that it should be possible

to suppress it. Even if one accepts Burnet's concept of a clone of cells separated from the rest of the body, their difference from normal cells must be such that man still has ample opportunity to interfere with them, to suppress them, or destroy them even if he cannot restore them to normal.—I am, etc.,

Kingston Hospital, Kingston-upon-Thames. D. Stark Murray.

Dilatation and Curettage

Sir,—Mr. W. C. Spackman (*Journal*, October 24, p. 827) does a considerable service in drawing attention to the often haphazard indications for this operation, and the frequent brutality in its performance. I myself frequently use the aphorism that, after childbirth, the commonest cause of backache in women is the lithotomy position, and the commonest cause of cervical discharge the operation of dilatation. This last is, of course, a euphemism—no nulliparous cervix will stretch beyond No. 8 Hegar—after that the rupture so graphically described by Mr. Spackman begins.

In the average case this danger is of little importance, for it is rarely necessary to exceed No. 8 for adequate exploratory curettage. But in the very tight cervix occasionally encountered rupture may occur at even lower degrees, particularly when the bullet-nosed Hegar type of instrument is employed. This can be avoided by using the special dilator I described some time ago,[1] in which the graduation is much more extended and less abrupt, allowing of effortless stretching, in place of the usual forcible push and sudden release of older types. The double-ended variety of the latter are even less efficient, for apart from their surgical dirtiness they are apt to slip around in the hand as the lubricated second half is grasped.

Mr. Spackman is also correct in suggesting that the operation is probably performed too frequently and for inadequate indication. Most erosions and chronic cervical discharges will react as well to appropriate antibiotic pessaries as to dilatation and cauterization, and endometrial biopsy for sterility or hormonal dysfunction can often be carried out without dilatation or anaesthesia by using one of the fine curettes designed for this purpose. Apart from these cases, however, I would regret too much limitation on the use of the operation, for it is surprising how frequently an unexpected endometrial polyp, a small submucous fibroid, or a long-retained conceptional product is relieved by this means. Carcinoma of the body is less likely to be missed, but an atypical history at the premenopause can only be elucidated by curettage, for both vaginal smears and hysterography can be equivocal in such cases.

Lastly a word about the mumbo-jumbory associated with this oldest of operations. It is surely unnecessary to admit the patient two or three days beforehand, shave off her vulval and suprapubic hair, pass catheters, and administer enemas, paint her posterior in rainbow hue, and keep her in subsequently for five days, as is the general practice. A simple hair-clipping will obviate the prolonged discomfort of regrowing hair, enemas are surely superfluous, and minimal preparation of the skin with iodine, with surgical spirit to clear away mucus in the vagina, provide adequate antisepsis. (Do surgeons never read the annotations on skin antiseptics which appear with yearly regularity in the *Journal*, and which monotonously reiterate the comparative worthlessness of these dyes?) And the maximum stay of three days, which is all that is necessary, will go a long way to solving the gynaecological bed problem.—I am, etc.,

London, W.1. Albert Davis.

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Birth Weight and Maternal Smoking

Sir,—Chastened by Dr. D. F. Hawkins's letter (*Journal*, October 24, p. 820), I am glad to bow to those who remind us that an association between two observations such as smoking and birth weight does not prove that the one causes the other. But interpretation of numerical or any other kind of evidence requires that the investigator shall use his common sense. Had I reported that mothers fed on haggis to the music of bagpipes had small babies, others as well as Dr. Hawkins might have been sceptical. But, in the light of experimental evidence that pregnant rats and rabbits exposed to tobacco smoke produce small offspring, the conclusion "that smoking during pregnancy substantially retards foetal growth" seems not unreasonable.—I am, etc.,

Department of Social Medicine, The Medical School, Birmingham, 15. C. R. Lowe.

Treatment of Migraine

Sir,—On the subject of the treatment of migraine I feel entitled to speak, as I have suffered from it to a greater degree than any case I have ever seen. I disagree with Dr. Christopher Heath's opinion (*Journal*, October 17, p. 759) that its manifestations are aggravated by relaxation, and I don't think it at all likely that any migraine subject would go to bed with a slight attack. I have noted that any severe strain is followed by an attack in 48 hours. Quite a small annoyance during a meal is followed by one in 48 hours. A holiday cures the liability at once and for some time after.

Migraine subjects are unlikely to follow any advice to lie down with a slight attack. I have never known of a case that did. One dreads lying down, always hoping to avoid reaching the state where one cannot stand up. It is due to some trigger mechanism or conditioned reflex. "Stemetil" (prochlorperazine dimaleate) or "fentazin" (perphenazine) keeps some cases free; phenobarbitone is sufficient for some. Others can only become acquainted with their trigger and take the remedy on the one or two nights after the trigger is pulled and so abort the expected attack. To remove stress would remove a stress trigger. Lucky are those who can do just that.—I am, etc.,

New Milton, Hants. Mary G. H. Edwards.

New Sulphonamides

Sir,—I have read with interest the letter by Dr. David Wheatley (*Journal*, October 10, p. 694) which recorded the trial in general practice of sulphaphenazole.

It should be pointed out that, though a sulphonamide may be a cheaper form of treatment for chronic bronchitis, it has not been found to be an effective form of treatment.

In 1953, a trial by Elmes *et al.*,[1] using chlortetracycline, penicillin, chloramphenicol, and sulphadimidine, showed that, "although each drug, except sulphadimidine, temporarily reduced bacterial counts and the purulence of the sputum, the clinical effects were slight." . . . "For various reasons none of the drugs appeared suitable for the prophylaxis of acute exacerbations." In this trial, the sulphonamide was found to be of little value in the treatment of bronchitis in its chronic form. In 1957, Edwards *et al.*[2] reported that "continuous

administration of oxytetracycline is shown to be an effective measure in the treatment of chronic bronchitis. The improvement arising therefrom is considerable, and the results are enhanced by the addition of a sulphonamide." . . . "The use of a sulphonamide alone is of little value." This trial stated that a sulphonamide, by itself, was of little value; but that, in combination with a tetracycline, the sulphonamide was of greater use.

From the work of these clinicians it would appear that sulphonamides are not the answer to the treatment of chronic bronchitis, despite their relative cheapness. Edwards and Fear,[3] reported in October, 1958, after a trial with tetracyclines, "It is suggested that continuous therapy with oxytetracycline for one period of about six months in each year, to include the period of maximum relapse, may prevent exacerbations and maintain most bronchitics in effective and useful employment."—I am, etc.,

Rochester, Kent. J. R. HARPER-SMITH.

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Organic Aetiology in Psychiatry

SIR,—To mark my retirement from Health Service consultant psychiatry and to admonish against the still-too-prevalent teaching of some psychiatrists in this country that in every case of mental illness there must be an organic cause, may I through your columns draw to the attention of your readers the following true story?

A few years ago at a meeting of the Royal Medico-Psychological Association I endeavoured to explain, upon a basis of unconscious dynamic understanding, the forces which led a sufferer from a severe compulsive neurosis to commit triple murder. At the tea interval a then most distinguished figure in British psychiatry approached me, saying, "Unless you are prepared to admit that there must be an organic cause underlying this behaviour, this is where you and I part company." We parted company.

A few days later he phoned our hospital and suggested to the then medical superintendent that we ought to have the patient's jaws *x*-rayed for the possibility of unerupted wisdom teeth being that cause. When the superintendent told me this, incredulously, I gasped, "Did he really say that? Because if so I am beginning to understand why British psychiatry has stuck in the rut for so long." The jaws were duly *x*-rayed, but no unerupted wisdom teeth were found.

Britain has still much to learn from America, who apply the teachings of Freud regarding the importance of unconscious dynamic factors, not only in psychiatry, but in the understanding of the problems which beset general practitioner and those in other medical specialties alike. In the mental hospital health service to-day an analytical approach to the understanding of the mind is regarded as a luxury which cannot be afforded. A superficial approach together with symptomatic treatment must suffice: thus equality of insufficiency and limited good for the many is attained.

I submit that the medical curriculum needs to be radically amended, specific instruction in psychosomatic correlations being given immediately the student attains access to the wards and thereafter throughout. The innate conservatism of the Royal College of Physicians lies at the heart of this problem, and, if I may do so without irreverence, I would suggest that that venerable foundation needs to reorientate and bring up to date its attitude lest over-regard for the traditional should lead to its remaining archaic.—I am, etc.,

Croydon. WILLIAM H. SHEPLEY.

Synnematin B in Typhoid Fever

SIR,—In an annotation in the *Journal* of October 3 (p. 628) the use of cephalosporin N (synnematin B) in typhoid fever was mentioned. The reference you gave was merely to Florey.[1] It might be mentioned that the substance was discovered to be a penicillin by myself in 1949. With some colleagues, who later helped in the project, a note was published in *Nature*[2] in February, 1953. The very name cephalosporin N is my designation for the substance, which was mentioned in an earlier publication.[3]—I am, etc.,

Oxford. H. S. BURTON.

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Artificial Insemination

SIR,—I was amazed to read the penultimate paragraph of the otherwise sensible proposals of the Law Society relating to artificial insemination (*Journal*, September 26, p. 584). Apart altogether from the moral and social implications of offering A.I.D. to unmarried women, one must consider the unhappily not uncommon case of the scheming woman who regards pregnancy as the key to matrimony. To her, pregnancy is merely a means to this end, and the Law Society's proposal would surely help her should the more usual method fail.

Although the proposals embody legal safeguards, nevertheless the onset of pregnancy in a woman "at risk" might well be sufficient to precipitate marriage, without the putative father even considering the possibility of the pregnancy being the result of A.I.D. I wonder if the Law Society considered this aspect before submitting their memorandum.—I am, etc.,

Free Hospital for Women, Brookline, 46, Massachusetts. MICHAEL GALTON.

Stocky Eyes and Pain

SIR,—When a student, working in the casualty department, I eased my burden considerably by always selecting blue-eyed and fair-haired children as my share of painful dressings.[1] Nordic children either have a higher pain-threshold than other children or greater self-control. I suspect the latter. At times it approaches serenity. The Nordic girl is better than the boy.

In a study of growing-pains involving about a thousand children I found blue-eyed children less frequently affected than the rest.[2 3] One considered reason for this was a higher pain-threshold or else lessened tendency to complain of pain. My figures in relation to these "Nordics" were statistically significant, but the records were destroyed in the 1940 blitz on London, so the results were never published. I suspect one reason for the serenity of Nordic children is the tranquil home-life which Nordics are wont to live.—I am, etc.,

London, N.W.8. J. C. HAWKSLEY.

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Obituary

J. C. MEAKINS, C.B.E., M.D., C.M., LL.D.

F.R.C.P., F.R.C.P.Ed., F.R.C.P.C., Hon.F.R.C.S.Ed., F.A.C.P.

Professor Jonathan Meakins, emeritus professor of medicine in McGill University, died at the Royal Victoria Hospital, Montreal, on October 12. He was 77 years of age.

Jonathan Campbell Meakins was born at Hamilton, Ontario, on May 18, 1882, and graduated in medicine at McGill University in 1904. After graduation he held the appointments of resident physician at the Royal Victoria Hospital, Montreal (1904–06), assistant in medicine at Johns Hopkins Hospital, Baltimore (1906–07), and resident pathologist at the Presbyterian Hospital, New York (1907–10). He then returned to Montreal, where he became assistant physician to the Royal Victoria Hospital, and lecturer in medicine and pathology in McGill University, holding the appointments until 1913, when he took up studies in London under Sir James Mackenzie and Sir Thomas Lewis. After the first world war, in which he served with the Royal Canadian Army Medical Corps, attaining the rank of lieutenant-colonel, he resumed his duties at McGill in 1918. In the following year he was appointed Christison professor of therapeutics and clinical medicine at Edinburgh University. He also became director of the medical research laboratories in the university and in the Royal Infirmary in 1920, and in 1923 he was appointed consulting physician to the Royal Maternity Hospital.

In 1924 Meakins returned to Montreal, and was appointed director of the department of medicine and professor of medicine in McGill University. Later he became director of the university clinic at McGill and chief physician to the Royal Victoria Hospital. He was elected the first president of the Royal College of Physicians and Surgeons of Canada in 1929, and held office until 1931; he was president of the American College of Physicians in 1934–5; and president of the Canadian Medical Association in 1935–6. In the second world war he was appointed deputy director of medical services in the Canadian Army, with the rank of brigadier. In 1942 he was appointed dean of the faculty of medicine in McGill University, but was granted leave of absence until his return from the army in 1945. In that year he was appointed C.B.E. Two years later he retired from his university and hospital posts, but continued his interest in hospital and research work, serving as chairman of the medical board of the Royal Edward Institute and the Grace Dart Hospital, both hospitals devoted to tuberculosis.

In the course of his career Meakins received many recognitions of his eminence in the field of medicine. He was an honorary LL.D. of Edinburgh and an honorary M.D. of Sydney: he was admitted a Fellow of the Royal College of Physicians of Edinburgh in 1919 and a Fellow of the Royal College of Physicians of London in 1935; he was a Fellow of the Royal College of Physicians of Canada and of the American College of Physicians; he was an honorary Fellow of the Royal College of Surgeons of Edinburgh and of the Royal Society of Medicine; and he was a Fellow of the Royal Society of Edinburgh and of the Royal Society of Canada. When the British Medical Association held its Annual Meeting at Newcastle upon Tyne in 1921 he served as a vice-president of the Section of Physiology, Pharmacology, Therapeutics, and Dietetics. He had a genius for organization and the stimulation of research, and his writings in the medical field were extensive. One of his first publications was entitled *Respiratory Function in Disease*, which he wrote jointly with W. H. Davies, and his *Practice of Medicine* went to six editions. He was editor of the *American Heart Journal* from 1950 to 1958. He was twice married. First, in 1911, to Miss Dorothy Brown, by whom he had three children, and secondly, in 1928, to Miss Sara C. Young, who survives him. His son is a senior attending physician at the Royal Victoria Hospital, Montreal.

F. R. F. writes: Jonathan Meakins's professional career was almost an epitome of the developments in medical education during the first half of this century. His undergraduate training at McGill University was at that time as good an example of the English traditional clinical training as was to be found in the American continent. From there he moved to Johns Hopkins where he took part in that wonderful and successful experiment under Welch, Osler, and their colleagues in insisting on university standards of research and teaching in the clinical departments of a medical school. After three further years' training in the pathology laboratories of the Presbyterian Hospital in New York he returned to Montreal as director of experimental medicine. There he introduced to Canada the scientific clinical medicine of Baltimore.

It was while serving as medical consultant to the Canadian Army Medical Corps in the first world war that he came to know and be known to leaders of the medical profession in the United Kingdom. His tall, lean figure, his training in academic medicine, his ability to encourage and guide his juniors, and his sound common sense made him a person of importance during the period of recovery from the disturbed conditions of medical education at the end of the war. The University of Edinburgh was fortunate to obtain him as first Christison Professor of Therapeutics, but he was hardly there long enough to influence the medical school to the extent he would surely have succeeded in doing. McGill and the Royal Victoria Hospital, Montreal, claimed him, and he returned there in 1924 as professor of medicine, director of the department of medicine in the hospital, and Dean of the Faculty. In this position he was able to develop and demonstrate the value of a team of young, enthusiastic, laboratory-trained assistants in the education and training of clinicians, devoted to teaching and research. This is what he was trained for and to this he devoted his career.

Inevitably his time, when not occupied by his teaching and hospital duties, became more and more in demand for committee work and administration in connexion with the university and professional bodies. He was President of the Royal College of Physicians and Surgeons of Canada, of the Canadian Medical Association, and of the American College of Physicians. He was forceful and uncompromising in discussions, for he knew what is good in medical practice and education. He was both a product and a supporter of clinical science in the years when it was struggling for university recognition. Following his retirement from McGill he found much to interest and occupy him in literature and the arts.

Dr. T. F. COTTON writes: Jonathan Meakins died in the Royal Victoria Hospital, Montreal, last October in his 78th year. He had hoped to be at a class reunion that month which I could not attend. We were friends for 50 years; he was my senior, having graduated at McGill five years before me. Nearly all his professional life was in the hospital where he died. There were periods when we were in close contact, but in recent years distance kept us apart. He and Paul White followed me to work with Lewis at U.C.H. Later during the first world war he was one of a team directed by Lewis at the Hampstead Heart Hospital, seconded from the C.A.M.C. like me, was recalled and placed in charge of medical services at Taplow. For a short period after the war he returned to this country to occupy the Chair of Therapeutics and Clinical Medicine at Edinburgh. He was recalled to be made Director of the Medical Department of the R.V.H., and later Dean of the Medical School and there remained until retirement. During this period his *Practice of Medicine* became a worthy successor of Osler's *Practice of Medicine*, and might easily be considered a leading textbook on the American continent and elsewhere. Thus his Canadian-American relationship was closely integrated. This integration was supported by his editorship of the *American Heart Journal*.

Meakins began as Jack, later John, finally Jonathan, and during these changes in nomenclature he climbed the ladder of fame, always in an upward direction. He seemed to have his objectives within reach and rarely fell short of his aim. He excelled as an administrator and directed his activities not always with a gloved hand. He belonged to the laboratory, his first love, and perhaps consequently lacked some of the qualities of a great clinician. His literary style was not Osler's, which is reserved for a few in our profession. He had not the creative qualities of Haldane and Barcroft, with whom he collaborated at one period, but could synchronize his work with that of others, always a correct procedure, hence he had a wide knowledge of medicine. He has long passed Osler's fixed period !

His career was an academic one, sheltered from the turmoil of consulting practice, and therefore he could direct all his energy to what some may say matters most.

S. J. CAMERON, LL.D., M.B., Ch.B.
F.R.F.P.S., F.R.C.O.G.

Professor S. J. Cameron, emeritus professor of midwifery in the University of Glasgow, died at his home at Strathaven, Lanarkshire, on October 29. He was 81 years of age.

Samuel James Cameron was born on January 7, 1878, the son of Professor Murdoch Cameron, who also became emeritus professor of midwifery in Glasgow University. He was educated at Mill Hill School and at Glasgow University, where he graduated M.B., Ch.B., with commendation, in 1901. Elected a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1916, he became a founder Fellow of the Royal College of Obstetricians and Gynaecologists in 1929. After graduation he held a house appointment in the gynaecological ward at Glasgow Royal Infirmary, and afterwards was lecturer in clinical obstetrics and assistant to the Regius professor of midwifery. Thus, from the outset of his career, he elected to follow in his father's footsteps. He became obstetric surgeon and gynaecologist to the Glasgow Maternity and Women's Hospital and to Bellshill Hospital, obstetric surgeon to Motherwell Maternity Hospital, obstetrician to the Perth Maternity Hospital, and gynaecologist to the Western Infirmary, Glasgow. Ultimately, he became consultant to all these institutions.

In 1934 Cameron succeeded Professor J. M. Munro Kerr as Regius professor of midwifery in the University of Glasgow, and occupied the chair until 1943, when he retired. The title of emeritus professor was then conferred upon him, and in the following year he received the honorary degree of LL.D. of the university. He was the author or joint author of a number of textbooks on obstetrics and gynaecology, and for many years he edited the *Glasgow Manual of Obstetrics*. He had also examined in his subjects for St. Andrews University, and he was a past president of the Glasgow Obstetrical and Gynaecological Society. A member of the British Medical Association for 55 years, he acted as one of the honorary secretaries of the Section of Obstetrics and Gynaecology when the Association held its Annual Meeting at Glasgow in 1922.

J. H. writes: Professor S. J. Cameron was one of the most distinguished members of the Glasgow school of medicine in the past quarter of a century. The mere list of the appointments he held indicates what a busy life he led, but it does not show the wide range of his interests and the full scope of his activities. It is now 16 years since he retired from active practice, and many of the junior obstetricians in the Glasgow school never knew him personally, but his name is already a legend among them. For the most part they think of him as a man of vast clinical experience, great diagnostic powers, and of supreme speed and dexterity in operating. This, however, is only one aspect of his work and probably not the most important.

During his life Professor Cameron set himself a number of tasks, and, unlike most people, he succeeded in accomplishing the majority of them. For instance, it was one of his ambitions to become a teacher, and he did in fact excel in this direction. He followed his father, after an interval of time, in the Regius chair of obstetrics at Glasgow University; he provided for students and practitioners a textbook on gynaecology and one on midwifery, and for specialist obstetricians two volumes of a more advanced nature. Secondly, in the course of his extensive practice he noted the absence of obstetric facilities in the populous county of Lanarkshire and in the rural counties between Carlisle and Stranraer, and by his personal efforts he founded, and to a large extent developed, the excellent obstetric services which exist in these areas to-day. Again, as an ardent admirer of William Smellie, he regretted the neglect of such relics as remained, and, by interesting the authorities concerned, secured a proper home for the Smellie library, and instigated the obstetric societies of Edinburgh and Glasgow to renovate Smellie's tomb and build a suitable protection for it. Lastly, he secured the establishment of a maternity hospital in Lanark and arranged that it should be called the Smellie Memorial Hospital, and as a personal gift he presented the lovely bronze statue memorial of mother and child which stands in the grounds of the hospital.

Only a man of great energy and powerful physique could possibly have accomplished so much, but Professor Cameron worked so easily and speedily that he found time for many other things. He was a keen sportsman, indulging in sailing, fishing, and shooting, and he was a lover of nature and a student of the ways of all manner of animals—both wild and domestic. He read widely; he was versed in the local folklore of Lanarkshire and in the histories of famous Scottish families. In addition, he was a connoisseur and collected all manner of art treasures, and his lovely home at Stobieside was filled with beautiful specimens of silver, old furniture, etchings, mezzotints, and paintings—many of them the works of the great masters. In brief, he exemplified all that was best in the bygone age of culture and gracious living. Yet with it all he was humble, unassuming, and friendly; everyone was welcome to his home—his colleagues, his juniors, and the farmers and the farm workers from the surrounding district—and all were treated with the same generosity and courtesy. His home was indeed his greatest pleasure, and no man ever had a happier married life or family life than he. To his widow and children—a son and three daughters—we extend our sympathy.

Sir JAMES ELLIOTT, M.D., LL.D., F.R.A.C.S.
F.A.C.S.

Sir James Elliott, an eminent New Zealand surgeon, and editor of the *New Zealand Medical Journal* for over 20 years, died on October 28. He was 79 years of age.

James Sands Elliott was born at Randalstown, Northern Ireland, on May 28, 1880, the son of the Rev. James Kennedy Elliott, D.D. He received his early education in the United Kingdom and, later, at Wellington College, when his father moved to New Zealand. From Otago University he enrolled at Edinburgh University, but interrupted the study of medicine there to serve with the R.A.M.C. in South Africa, being awarded the Queen's medal with two clasps. He returned to Edinburgh and graduated M.B., Ch.B. in 1902, proceeding to the M.D. in 1912. After graduation he held the appointment of house-surgeon at Chichester Infirmary and then went back to New Zealand to become assistant resident medical officer at Wellington Hospital. Shortly afterwards he settled in practice in the city, becoming also public vaccinator for the district. Later, he was appointed honorary surgeon to Wellington Hospital, and, ultimately, honorary consulting surgeon. A keen Volunteer, Elliott held the rank of captain in the New Zealand Medical Corps by the time the first world war broke out in 1914. During the war he received promotion to lieutenant-colonel, and was in command of a hospital

ship. Subsequently he became assistant director of medical services for the Central Command in New Zealand. In the second world war he was chairman of the Joint Council of the Order of St. John and the New Zealand Red Cross Society from 1940 to 1945. He organized the New Zealand branch of the British Empire Cancer Campaign Society in 1929, and it was owing to his enthusiasm and drive that the society progressed with its work in establishing clinics and research laboratories in New Zealand. President of the New Zealand branch since its formation, he held this position for twenty-six years. In 1949 he represented the Dominion for the first time at a conference of the International Cancer Research Commission.

The culmination of his work for the Venerable Order of St. John of Jerusalem came in 1955, when he was created a Bailiff Grand Cross of the Order. The number of Bailiffs Grand Cross is limited to ten, exclusive of the Royal Family, and they are selected from Knights of the Order who are of eminence in the State or who have rendered conspicuously valuable and long-continued service to the Order. In the latter respect alone Elliott was worthy of the distinction, for he had served it for some fifty years. He began by delivering lectures in first aid in Wellington in 1906, and since then had held many responsible positions in the Order. From chairman of the St. John Ambulance Association in Wellington, he became a member of the Priory Chapter and then Chancellor of the Order, and attended its conference in London in 1949. He was a member of the committee which administered the four convalescent homes for Service men from 1919 to 1939. In this work he had in Lady Elliott one whose sympathies were identical with his own. She, too, attained high rank in the Order, being appointed a Dame in 1946.

When the Royal Australasian College of Surgeons was founded in 1926 Elliott was elected a foundation Fellow, and for a time he was a member of the editorial committee of the *Australian and New Zealand Journal of Surgery*, the official organ of the College. This latter appointment was one to which he brought a wealth of experience gained over many years as editor of the *New Zealand Medical Journal*, whose editorial chair he occupied from 1911 to 1933. He was elected a Fellow of the American College of Surgeons in 1924, and was a past-president of the New Zealand Branch and a past-chairman of the Wellington Division of the British Medical Association. Elliott also rendered public service of the most distinguished character as a member of the New Zealand Medical Council and of the Board of Health over a period of many years. He was created a knight in 1936, and three years later the honorary degree of LL.D. was conferred upon him by Aberdeen University as one who had "done his most outstanding work in the Dominion which is perhaps more closely linked to Scotland than any other member of the British Commonwealth." He married Miss Ann Allan Forbes in 1905 and had three sons, all of whom entered the medical profession, and one daughter.

JOHN LIVINGSTON, M.D., F.R.C.S.Ed.

Dr. J. Livingston, formerly honorary surgeon to the North Lonsdale Hospital, Barrow-in-Furness, died at his son's home at Ulverston, Lancashire, on June 16. He was 87 years of age.

John Livingston was born in 1871 at Lorne, Argyllshire. Educated at Oban, he went on to study medicine at Glasgow University, where he qualified in 1895. During the next four years he served as a medical officer in the Persian Gulf and with the P. & O. Steamship Company. Thereafter he studied for the Edinburgh Fellowship in surgery and was admitted a fellow of the Royal College of Surgeons of Edinburgh in February, 1901. He proceeded to the M.D. of Durham University in 1920. In addition to general practice, he found time to do general surgery and he was an honorary surgeon to the North Lonsdale Hospital for 37 years until he retired in 1948. During the first world war he served in the R.A.M.C. in France and was attached to the 56th casualty clearing station. Livingston was an active member of the British Medical Association for 56 years. He was Honorary Secretary of the Furness Division from 1908 to 1914 and of the North Lancs and South Westmorland Branch from 1914 to 1932, and Chairman of the Furness Division in 1921. He represented this Division on the Representative Body without a break from 1924 to 1947.

W. J. L. writes: John Livingston was a Highlander in the truest tradition. He was quiet, unassuming, and found time from a busy practice to be associated with many committees, in which he was greatly respected for his wisdom and well-considered advice. For many years he was a member of the governing board of the North Lonsdale Hospital and also of the Insurance Committee for Barrow-in-Furness. He was a life member and vice-president of the British Legion. He was also a strong Conservative. Perhaps one of his greatest interests outside his profession was the St. Andrew's Society, of which he was an active member for fifty years and became one of its most esteemed presidents. After retirement from practice constant ill-health kept him rather apart, and he had outlived all his colleagues. Among the younger generation he will be remembered for his rectitude, his directness in medical affairs, and his loyalty and kindliness to all who knew him. He is survived by his only son, with whom he had lived for the last fifteen years, and to him the profession in Barrow and district offer their sincerest sympathy.

T. O. JONES, L.R.C.P.&S.Ed.

Dr. T. O. Jones, who was the doyen of the medical profession in North Wales, died at his home near Ruthin, Denbighshire, on August 20. He was 88 years of age.

Thomas Owen Jones was born on May 8, 1871, and received his early education at the old St. Cybi's School, Holyhead, in his native county of Anglesey, but, like many of his compatriots of that period, he owed his medical training to Scotland. He took the Scottish triple qualification in 1894, and, after gaining experience in general practice elsewhere, settled at Ruthin in 1898. He soon won the confidence of the people in an area which not only embraced a busy market town but also some wild terrain. When in a reminiscent mood he would recount his experiences when visiting patients in the outlying parts of the district in bad weather. The superseding of the horse and trap by the motor-car brought its own problems of uncertainty of performance by the new form of transport, but no one appreciated more than he the development of the motor-car as a vehicle which could be relied upon, for he was a connoisseur of cars. Keenly interested in his chosen profession, he managed to keep abreast of advances in medical knowledge through the literature, attendance at medical meetings, and by seizing every opportunity to associate with colleagues at the hospitals serving the area. While always a practitioner of the art of medicine, he was quick to take advantage of modern scientific advances in diagnosis and treatment. For many years he took a personal interest in the North Wales Sanatorium at Llangwyfan and in the local hospitals.

In 1904 "Dr. T. O.," as he was known, was appointed the first part-time medical officer of health to the Ruthin Rural District Council, and he continued to serve in this capacity for 47 years. Many a village and hamlet in the extensive rural area for which he was responsible is to-day indebted to him for his pertinacity and his persuasive powers in the sponsoring of schemes which resulted in an improvement of rural living conditions. His experiences during the early years prompted him to take a practical interest in ambulance and home-nursing work, and his drive and enthusiasm played a major part in the provision of an ambulance and, later, a well-built and fully equipped headquarters for the St. John Ambulance Brigade and the Red Cross in Ruthin.

This fine building will be permanently associated with his memory. The borough of Ruthin honoured him by electing him mayor in 1908, and he held office for two years. In 1912 he became a member of the Denbighshire insurance and panel committees, and was chairman of the latter over a long period. His many years of unremitting service and leadership was recognized in 1949 by a presentation and dinner given in his honour by his colleagues in Denbighshire, but his long illness prevented the presentation, sponsored by the Ruthin Rural District Council, of a public testimonial in appreciation of nearly 60 years' service to the community. A member of the British Medical Association for 58 years, he was chairman of the Denbigh and Flint Division from 1931 to 1935, and president of the North Wales Branch in 1942–3. In 1948, on the formation of the local medical committee for the counties of Denbigh and Flint, he was elected vice-chairman and representative on the executive council, but infirmity caused him to resign in 1951. He then became an "elder statesman" to whom his younger colleagues turned for advice and guidance. During the earlier part of his 60 years in active practice he was able to work single-handed, but, later, when he had to engage assistants, he passed on the benefits of his wide experience and clinical acumen to younger men, including, eventually, his two sons. He suffered a grievous loss in the untimely death of his elder son, and it was a great joy to him when his other son was able to join him in the practice. He officially retired when over 80 years of age, but this did not deter him from taking an active interest in the welfare of his old patients. He was able to enjoy the leisure which he so well deserved until the advent of a long and trying illness, during which he was devotedly cared for by his family. It was at this period in his life that he became fully aware of the full extent of the gratitude and affection of his many friends. Many of his colleagues gratefully remember the hospitality and welcome extended to them by his family, for his home was often the centre of an interesting and informal medical "get together." He will long be remembered in this part of the principality as a fine type of family doctor, a sound clinician, an able physician, and a wise leader in his profession. To his widow and the family, his many medical colleagues and friends offer their sympathy in their bereavement.—I. H. D.

A. W. H. writes: "Dr. T. O." had few hobbies, but, as one patient put it, "He enjoyed the luxury of doing good." Immaculate in dress and manner, he was a good, friendly family doctor, and never failed to respond to an urgent call at any hour in any weather. Some of his patients lived in wild and bleak country, and in the old days it was not unusual in very severe weather for a sledge to be requisitioned as the form of transport. Widely known throughout North Wales, he was well-beloved among his patients and greatly esteemed among his colleagues. He practised medicine for 60 years, and then enjoyed for some further time a well-earned but active leisure until the advent of the last long and trying illness, when he was so devotedly cared for by his family.

L. S. BRUCE, M.B., Ch.B.

Dr. L. S. Bruce, who had been in general practice at Blairgowrie, Perthshire, since 1951, was killed in a motor-car accident in France on August 26. His wife and two children, who were in the car with him, were slightly injured. He was 44 years of age.

Lewis Stuart Bruce was born on January 2, 1915, the son of Dr. L. C. Bruce, physician-superintendent of the Perthshire Asylum, Murthly. Educated at Glenalmond and at Edinburgh University, he graduated M.B., Ch.B. in 1939. After holding house appointments at the Victoria Infirmary, Glasgow, and at the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, he joined the R.A.M.C. in 1942, serving first in East Africa, and, later, with a parachute field ambulance in Italy, Greece, and Palestine. During his war service he contracted amoebiasis, which severely affected his health for a long time afterwards. After the war he held junior surgical appointments at Edinburgh Royal Infirmary and at Stracathro Hospital. In 1950–1 he was surgical registrar at Lewis Hospital, Stornoway, where he showed himself to be a capable surgeon. In 1951 he entered practice at Blairgowrie with Dr. M. M. Shepherd.

P. C. M. writes: Stuart Bruce was a fine athlete and captained the Edinburgh University cross-country eight. He was a keen piper and an accomplished dry-fly fisherman. He had a strong personality, holding decided views on almost every subject. He will be most remembered for his straightforward character and his transparent honesty. He was incapable of doing or saying anything petty. His decisive manner and direct approach were well suited to the character of the people he cared for, and brought confidence, calm, and comfort into homes where there was illness. Our sympathy goes out to his widow, who loyally supported him in everything he did, and to his two children. He will be sadly missed in East Perthshire, where he, and his parents before him, had established a tradition of public service lasting over sixty years.

Medical Notes in Parliament

POINTERS FOR THE NEW SESSION

Two points in the programme for the first session of the new Parliament attract attention. The first is the fulfilment of the promise in the Conservative Party's election manifesto to bring scientific research and development under unified direction. In the words of the Queen's Speech, "in recognition of the place of science and technology in the modern world a Cabinet Minister has been entrusted with the task of co-ordinating and promoting development in research and other scientific activity." This Minister is Viscount Hailsham, appointed Lord Privy Seal in the new Cabinet, and since confirmed in the new office of Minister for Science.

Minister for Science

The PRIME MINISTER, commenting on this innovation in his first speech on October 27, said that Lord Hailsham would be giving his undivided attention to the various problems involved in the relationship between Government and science. His role would be "to advise, to help, and to stimulate, rather than to control." That was why he had been called Minister "for" and not "of" Science. An Order in Council on October 31 transferred to the new Minister, who will have a small administrative staff which will be known as the Office of the Minister for Science, functions previously carried out by the Prime Minister and the Lord President of the Council. From the Prime Minister he takes over duties under the Atomic Energy Acts; and he becomes, in place of the Lord President, chairman of the Privy Council committees for the five research councils. These are the Council for Scientific and Industrial Research, the Medical Research Council, the Agricultural Research Council, the Overseas Research Council, and the Nature Conservancy. To all this is added a general supervision over the programme of space research being devised under a steering group presided over by Sir Edward Bullard. Other Ministers, the Prime Minister has explained, remain responsible for the scientific establishments within their own departments, but the

Minister for Science is responsible for broad questions of scientific policy outside the sphere of defence, and is advised by the Advisory Council on Scientific Policy.

Mental Health and Registration of Auxiliaries

The other point that claims notice is the announced intention of the Government to give close attention to social welfare, which, in addition to matters such as housing and pensioners' earnings, includes specific mention of a Mental Health Bill for Scotland, and a Bill "providing for the registration of certain professions auxiliary to medicine." This passage formed the theme of an attractive maiden speech on October 28 by Mr. LAURENCE PAVITT, the new Labour member returned by Willesden West, and national organizer of the Medical Practitioners' Union.

He had hoped to see the "close attention" expressed in some indication of improvements and changes in the Health Service, and sought to fill the gap by offering some himself. He had been very fortunate, he said, in attending most of the public hearings of the Royal Commission on the Remuneration of National Health Service Doctors and Dentists; he had been impressed by the way it was tackling its formidable task, and he hoped its report would come this session.

Burden on the G.P.

Mr. Pavitt urged that the time had come when the burden resting on the general practitioners should be eased; there was a strong case for reducing the number of patients on the doctor's list, so that there could be more time for diagnosis and determination of therapy. He wanted a working party set up by the Government and the profession to secure such a reduction in an orderly and co-operative manner. He wanted also an extension of group practice, and more positive incentives for it; starting with a team of doctors and then putting round them the equipment and buildings. He wanted surgeries and waiting-rooms brought up to reasonable standards, and an extension of the appointments system for patients. He wanted better organization in out-patient departments to prevent people having to wait about; and a reduction in the waiting time before admission to hospital for treatment. Finally, he advocated the establishment of an occupational health sector, pointing his argument with a delightful personal touch: "At this moment I can speak with real feeling of the nervous strains and hazards of a man's occupation."

All this, as Mr. Pavitt indicated, will be canvassed and discussed again as the Bills and the Estimates come upon the scene. So, too, will the question of free drugs for private patients, on which Sir OTHO PRIOR-PALMER (Worthing, Con.) found a supporter in Mr. ERIC JOHNSON (Manchester, Blackley, Con.), but got into trouble with Dr. EDITH SUMMERSKILL (Warrington, Lab.) on the issue of creating two classes of patient.

QUESTIONS IN THE COMMONS

Toxic Agricultural Sprays

Mr. BARNETT JANNER (Leicester, North-west, Lab.) asked the Minister of Agriculture, Fisheries and Food on November 2, in view of the recent verdict of death by misadventure on a woman who died after drinking water contaminated by an arsenical potato-spray mixture, what action he proposed to take with regard to the coroner's recommendation that these arsenical sprays should be prohibited.

Mr. J. HARE replied that this matter had been urgently considered by the Advisory Committee on Poisonous Substances used in Agriculture and Food Storage, whose recommendations were now being discussed with the agricultural and chemical industries. He hoped to be in a position to make a statement shortly.

Health Hazards of Pottery Industry

Dr. BARNET STROSS (Stoke-on-Trent Central, Lab.) asked the Minister of Labour whether he was aware that the Survey of the Pottery Industry, published in 1959, had demonstrated that there were considerable health hazards in some of the processes; and what action had been taken to reduce the incidence of pneumoconiosis and dermatitis, and to promote the health and welfare of pottery workers generally.

Mr. PETER THOMAS, the Parliamentary Secretary, stated that the outstanding problems indicated in the report were under examination by the Joint Standing Committee of the Pottery Industry, to which the report had been referred. The Factory Inspectorate was following up particular cases in the ordinary way to secure improvements.

Dr. STROSS asked how many cases of lead poisoning had been diagnosed in the pottery industry since 1952; and for details of the process involved in any recent case. Mr. PETER THOMAS informed him that two cases had been notified, both in 1958. Full details were given in the annual report of the Chief Inspector of Factories on Industrial Health for that year.

Polio Vaccination in Armed Forces

Mr. M. LINDSAY (Solihull, Con.) asked the Minister of Defence what was his policy in regard to poliomyelitis inoculation for men and women in the armed Forces. Mr. HAROLD WATKINSON stated that members of the Forces had the same opportunities as civilians. Up to now, all men and women under the age of 26 who had volunteered had been inoculated. As more vaccine was now available, this age limit was being removed.

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Oct. 17	Week Ending Oct. 24
Continued Fever		
Glasgow	1	5
Acute Poliomyelitis		
London	3	4
Lewisham	0	2
Lancashire	2	5
Dysentery		
Berkshire	19	34
Bradfield R.D.	16	33
Hampshire	6	18
Bournemouth C.B.	1	11
Lancashire	101	93
Liverpool C.B.	23	26
Worsley U.D.	8	26
London	37	58
Battersea	1	10
Middlesex	6	21
Willesden M.B.	2	10
Shropshire	2	20
Atcham R.D.	0	19
Warwickshire	34	30
Coventry C.B.	22	15
Yorkshire North Riding	8	21
Middlesbrough C.B.	8	15
Yorkshire West Riding	87	122
Barnsley C.B.	17	19
Huddersfield C.B.	4	25
Leeds C.B.	26	37
Glasgow	195	182

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in September was 156, compared with 51 in the previous month and 104 in September, 1958.

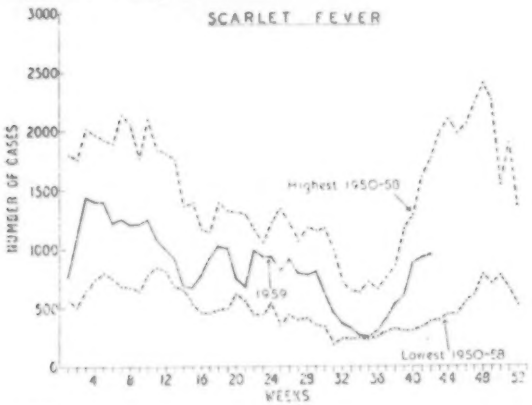
The numbers of cases of industrial diseases in the United Kingdom reported during September were as follows: Lead poisoning 4, aniline poisoning 9, anthrax 1, epitheliomatous ulceration 15, chrome ulceration 12; total 41. There were two deaths from epitheliomatous ulceration due to mineral oil.—*Ministry of Labour Gazette*, October, 1959.

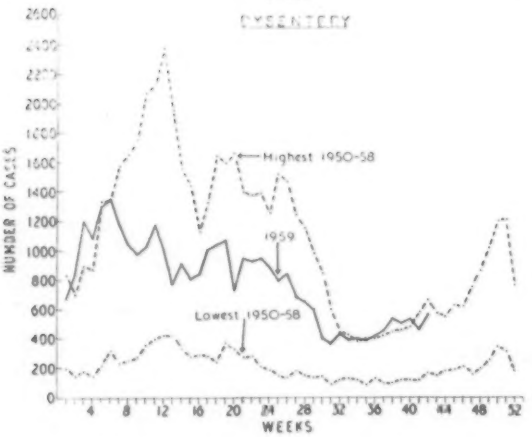
Venereal Diseases

In England and Wales during the quarter ending June 30, 1959, 929 new cases of syphilis were reported as attending the clinics, as compared with 1,055 the previous year. Of these, 170 were classified as primary, secondary, or latent in the first year of infection. 5 cases of congenital syphilis in children aged under 1 year were reported, and 77 cases in persons over that age. New cases of gonorrhoea (with corresponding 1958 figures in parentheses) numbered 8,165 (6,855), of chancroid 73 (64), and of non-gonococcal urethritis (males only) 5,257 (4,326).—*Monthly Bulletin of the Ministry of Health*, October, 1959.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 17** (No. 41) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	5	4	4	0		25	15	2	0	2
Dysentery	460	37	265	6	7	512	69	213	22	5
Encephalitis, acute	3	0		0		2	1		0	
Enteric fever:										
Typhoid	4	0	0	0		4	3	0	0	1
Paratyphoid	6	0	1(B)	0	2(B)	3	0	10 (B)	0	2(B)
Food-poisoning	248	19	15	0		229	35	92	2	
Infective enteritis or diarrhoea under 2 years				21	37				14	31
Measles*	959	25	17	39	60	2,778	164	22	9	53
Meningococcal infection	21	0	9	1	1	14	1	13	0	2
Ophthalmia neonatorum	15	3	3	0		34	7	6	0	1
Pneumonia†	252	19	119	0		216	9	123	2	1
Poliomyelitis, acute:										
Paralytic	18	1	0	} 2	4	{ 83	1	} 22	0	7
Non-paralytic	5	2	2			30	0			
Puerperal fever§	216	26	15	2		253	36	15	1	
Scarlet fever	918	46	123	28	28	648	47	114	20	15
Tuberculosis:										
Respiratory	424	52	60	18		484	62	76	16	
Non-respiratory	53	5	12	5		49	5	14	7	
Whooping-cough	502	35	100	4	28	500	26	74	58	35

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0	1	0	1	0	2	1	0
Influenza	11	0	1	0	0	7	1	1	1	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	356	28	17	6	6	364	17	21	8	3
Poliomyelitis, acute	3	1		0	0	5	1	1	0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 71	{ 5	3	2	0	} 70	{ 9	7	1	2
Non-respiratory		0	2	0	1		1	1	0	0
Whooping-cough	0	0	0	0	0	1	0	0	0	0
Deaths 0–1 year	193	33	27	7	7	275	27	30	3	11
Deaths (excluding stillbirths)	8,339	631	500	118	143	8,760	696	500	91	142
LIVE BIRTHS	14,182	1185	1012	240	358	14,960	1239	516	235	388
STILLBIRTHS	270	18	26			296	24	28		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Medical Research Council of Ireland

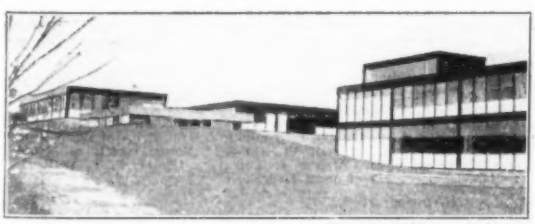
The Council's *Annual Report for 1958* discloses how seriously its activities are restricted by the smallness of the funds received from the Ministry of Health. A deputation to the Minister in January, 1958, estimated that the annual grant of £23,000 would need to be doubled if projects, including a study of cell metabolism, which the Council was anxious to support, were to be carried out. However, the most the Minister felt able to offer was an annual increase of £4,000, giving a total of £27,000 for the next five years. This, the Council suggests, does little more than cover the rise in the cost of living, and unless conditions improve it foresees an inevitable contraction of its activities.

Christmas Cards

Unicef's colourful cards have been designed this year by artists from Britain, Denmark, Hungary, America, and Spain. They cost 7s. 6d. for 10, and they, and a leaflet illustrating them, are obtainable from Unicef Greeting Card Fund, 14–15, Stratford Place, London, W.1 (MAY 3749). Proceeds from last year's sales supported Unicef help to 97 countries for 10 days. The National Deaf Children's Society's card, of the Christ child playing with robins, costs 3s. 6d. for six cards, from the Society, 1, Macklin Street, Drury Lane, London, W.C.2. The Invalid Children's Aid Association's three cards of traditional designs cost 8s., 7s., and 5s. for 12, and may be obtained from the association, 4, Palace Gate, London, W.8. The Grenfell Association sold 220,500 cards last year and made a net profit of £1,000. This year their very varied selection of cards with Arctic themes, including a "Madonna of the North," cost from 3d. to 9d. each. Cards and an illustrated brochure may be obtained from the Grenfell Association, 66, Victoria Street, London, S.W.1. The Imperial Cancer Research Fund, at the Royal College of Surgeons, London, W.C.2, has five cards available, designed by Anna Zinkeisen, and costing from 9s. a dozen.

Princess Margaret Hospital, Swindon

The first stage of the Princess Margaret Hospital which is shown here was opened by the chairman of Oxford Regional Hospital Board, Sir GEORGE SCHUSTER, on October 24. Costing £660,000, it includes the out-patient and casualty departments, orthopaedic ward, and physiotherapy and pathology departments of the complete hospital. It is hoped



[Powell and Moya : Architects

to start the second stage next year; this will be a multi-story 300-bed building, and will include a psychiatric ward, a theatre suite, and nurses' hostels with gardens. The third stage will have obstetric and paediatric units, and wards for old and chronically sick people. The present buildings have extensive views, and there are ornamental pools with fountains outside the wards.

British Student Tuberculosis Foundation

The several Units of the British Student Tuberculosis Foundation have now been brought together at Pinewood Hospital, Wokingham, Berkshire, to form a permanent centre, with 32 beds, for the treatment and rehabilitation of men and women students with tuberculosis. Students can continue their academic work at Pinewood, and, in some cases, take their examinations. The Library has over 3,000 books, and there are seven studies for private work. Inquiries should be addressed to the Secretary/Administrator, British Student Tuberculosis Foundation, Pinewood Hospital, Wokingham, Berkshire.

British Academy of Forensic Sciences

A British Academy of Forensic Sciences has been formed, with a steering committee under the chairmanship of Dr. LEON RADZINOWICZ, professor of criminology, University of Cambridge (see *Journal*, September 12, p. 443). The Society, which consists of three main sections—medicine, science, and law—will hold its first scientific meeting early next year.

The Committee includes representatives of the relevant disciplines and organizations in all three sections. The medical members of the committee are Dr. R. SUMMERS, Dr. C. H. JOHNSON (Association of Police Surgeons); Dr. G. STEWART-SMITH (Clinical Pathology); Dr. R. I. MILNE (Coroners Society); Dr. R. D. TEARE, Dr. F. E. CAMPS (Forensic Pathology); Professor R. HARRISON (Anatomy); and Professor D. KERR (Forensic Medicine).

Transatlantic Clinical Conference

On October 6 a transatlantic clinical conference by telephone cable was held between a team selected by the Sheffield Division of the B.M.A. and a team in Kansas City, where a three-day meeting of the Kansas South-west Medical Society was being held.

The Sheffield team consisted of Professor C. H. STUART-HARRIS (chairman), Professor P. R. ALLISON, Professor W. MELVILLE ARNOTT, and Dr. T. E. GUMPERT. The American team consisted of Professor C. THORPE RAY (chairman-moderator), Professor R. J. BING, Professor B. B. BLASE, and Professor E. S. ORGAIN. The Sheffield audience in the surgical lecture theatre of the Royal Infirmary considered the conference, organized by Smith, Kline and French Ltd., to be a great success.

"Epilepsia"

It has been evident for some time that the International League against Epilepsy needed a more flexible medium of communication than an annual volume, and it has been decided to issue *Epilepsia* as a quarterly journal, under the general editorship of Sir FRANCIS WALSHE, F.R.S. It is hoped that the journal will cover the fields of aetiology, pathogenesis, course, manifestations, investigations of every relevant kind, and treatment, both medical and surgical, and that it will encourage studies in the morbid anatomy of the epileptic brain. The overseas editors are Dr. HENRI GASTAUT (France), Dr. G. H. GLASER (U.S.A.), and Dr. A. M. LORENTZ DE HAAS (The Netherlands). Subscription rates are £2 17s., $8, or 30 Dutch florins, and inquiries should be sent to the publishers, Elsevier Publishing Company, 110, Spuisstraat, Amsterdam.

Royal Society Research Appointment

Dr. AINSLEY IGGO (department of physiology, Edinburgh University) has been appointed to a Locke Research Fellowship. Dr. Iggo will continue his research at Edinburgh on unmyelinated afferent nerve fibres, their peripheral specificity and their central connexions.

Guyot Prize

The University of Groningen has awarded the quinquennial 1959 Guyot Prize for the best work on otology to Dr. C. S. HALLPIKE, F.R.S., for his work on the auditory and vestibular organs. The prize is in memory of HENRI GUYOT, who founded the Institute of the Deaf and Dumb in Groningen in 1790.

Birmingham and Midland Medical Arts Society

It has been proposed that a Birmingham and Midland Medical Arts Society should be founded. Its aim will be to build up a collection of works by living artists for loan to members, who will also have the opportunity of purchasing them through the Society. Supporters are asked to get in touch with the Regional Office, 36, Harborne Road, Edgbaston, Birmingham, 15.

COMING EVENTS

Bradshaw Lecture: Royal College of Surgeons, England.—Mr. A. DICKSON WRIGHT: "Surgery of the Biliary Passages," November 12, 5 p.m., at the College, Lincoln's Inn Fields, W.C.2.

Edinburgh Pathological Club: First Clark Lecture.—Professor ALEXANDER HADDOW, F.R.S., "Direct and Indirect Mechanisms of Malignant Transformation," November 11, 5 p.m., Anatomy Theatre, University New Buildings.

National Association for Mental Health.—One-day conference, "Truancy—or School Phobia," November 13, Queen Mary Hall, Y.W.C.A. Central Club, Great Russell Street, London, W.C.1. Details from Public Information Organizer, N.A.M.H., 39, Queen Anne Street, London, W.1 (WEL 1272.)

Glasgow University Club, London.—Annual Dinner, Trocadero Restaurant, London, W.1, 7.30 p.m., November 26. Chairman: Sir DAVID CAMPBELL (president, General Medical Council). Non-member graduates should write to Dr. J. F. HEGGIE, Department of Pathology, North Middlesex Hospital, London, N.18.

Royal Faculty of Physicians and Surgeons, Glasgow.—Biennial dinner, Faculty Hall, 242, St. Vincent Street, Glasgow, C.2, November 27.

Symposium on "Wound Healing."—November 12 and 13, at Royal College of Surgeons, Lincoln's Inn Fields, London. Details from the sponsors, Smith and Nephew Research, Ltd., Hunsdon Laboratories, Ware, Herts.

Medical Group, Royal Photographic Society.—Exhibition of medical photography to be opened at the Society's house, 16, Prince's Gate, London, S.W.7, at 6.20 p.m., November 12. Open until November 19.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 9

GUY'S HOSPITAL.—At Physiology Lecture Theatre, 5.15 p.m., endocrine demonstration: Dwarfism.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Emotions and the Cardiovascular System.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. R. S. McNeill: Gas Diffusion in the Lungs and Abnormalities in the Alveolar Membrane and Capillary Bed.

Tuesday, November 10

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., joint meeting with British Psychological Society. Mr. P. R. F. Clarke: Sensory Deprivation.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor W. S. Peart: Some Aspects of Carcinoidosis.

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Mr. Donal Brooks: Problems of Tendon Grafting.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: Histochemistry of the Skin (I).

INSTITUTE OF NEUROLOGY—5.30 p.m., Professor A. Earl Walker (Baltimore, U.S.A.): Subcortical Mechanisms in Epilepsy.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 3.30 p.m., Mr. P. Rhodes: Some Aspects of Fluid Balance in Obstetrics.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. K. A. Exley: Pharmacology of the Ascending Reticular Activating System.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, Ashton Street, 7.30 p.m., Dr. H. Wilson: Actions of Drugs on the Autonomic Nervous System, with Special Reference to Drugs Acting on the Alimentary Tract.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., clinical evening. (Cases from 8 p.m.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. E. H. Belcher: Control of Radiation Hazards.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. D. M. Green: Immunological Methods and the Detection of Auto-antibodies.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. Richard Doll: Elements of Medical Statistics.

Wednesday, November 11

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Miss Enid Mills, B.A.: Psychiatric Patients and their Families in Bethnal Green.

CAMBRIDGE MEDICAL SOCIETY.—At Lecture Room, Addenbrooke's Hospital, 8.30 p.m., informal talk by a Television Engineer: Television in the Service of Medical Science. Members of Cambridge and Huntingdon Branch, B.M.A., are invited.

EDINBURGH PATHOLOGICAL CLUB.—At Anatomy Theatre, University New Buildings, 5 p.m., Clark Lecture by Professor Alexander Haddow, F.R.S.: Direct and Indirect Mechanisms of Malignant Transformation.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. A. Dudgeon: Virus Diseases (I).

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. H. R. S. Harley: Subphrenic Abscess.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. J. D. Fergusson: Cancer of the Prostate.

LISTERIAN SOCIETY.—At Lecture Theatre, King's College Hospital Medical School, 8.30 p.m. Sir Zachary Cope: Story of the Royal College of Surgeons of England.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Sir Victor Negus: The Voice of Man.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. W. G. Oakley: Disorders of Carbohydrate Metabolism.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. W. H. H. Merivale: Contribution of Laundering to Hygiene.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Royal Infirmary, Edinburgh, 5 p.m., Dr. B. O. L. Duke: Loiasis and Some of the Problems Relating to its Control.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Mr. W. F. Walker: Surgical Influence on Gastric Physiology.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Leeds General Infirmary, 8 p.m., Symposium on Cardiac Arrest and Cerebral Anoxia.

Thursday, November 12

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8 p.m., Dr. D. A. S. Blair: Relationship of Adler's Teachings to Other Schools of Psychiatry.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. M. H. F. Wilkins, F.R.S.: Molecular Structure of Chromosomes.

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Dr. Anne T. Lambie: Syndromes Associated with Potassium Depletion.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. F. Borrie: Erythema Nodosum.

INSTITUTE OF PSYCHIATRY.—At Maudsley Hospital, 5 p.m., public lecture by Professor A. Earl Walker: Modern View of the Falling Sickness.

PHYSICAL SOCIETY.—At Lecture Theatre, Science Museum, S.W., 5 p.m., 20th Thomas Young Oration by Professor R. W. Ditchburn: Problems of Visual Discrimination.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. T. Alper, Dr. M. Ebert, and Dr. R. H. Thomlinson: Biological Effects of Radiation.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Bradshaw Lecture by Mr. A. Dickson Wright: Surgery of the Biliary Passages.

ROYAL EYE HOSPITAL.—3.30 p.m., Dr. T. H. Whittington: Vision at Varying Distances. Accommodation.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION.—At Barnes Hall, Royal Society of Medicine, 2.15 p.m., 34th Maudsley Lecture by Professor Alfred Meyer: Emergent Patterns of the Pathology of Mental Disease.

ROYAL SOCIETY OF ARTS.—5.15 p.m., Mr. John Wilson: Blindness in the Commonwealth.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Mr. R. J. Brech: Medicine and the Rising Standard of Living.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: demonstration in neurology.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. P. N. Campbell: Synthesis of Protein by the Cytoplasmic Components of Animal Cells—(II) Intermediate Steps in the Synthesis of Proteins from Free Amino-acids.

Friday, November 13

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. M. B. MacKenna: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinico-physiological demonstration by Dr. N. Lloyd Rusby and Dr. L. H. Capel.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners. Mr. K. G. Rotter: Epistaxis. (2) 5.30 p.m., clinical lecture by Professor F. C. Ormerod: Pathology and Treatment of Deafness.

INSTITUTE OF NEUROLOGY.—4.45 p.m., Dr. R. W. Gilliatt: Syncope and the Neurologist.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, 4.30 p.m., Mr. W. G. Mills: Ancillary Aids to Gynaecological Diagnosis.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. G. L. Alexander: Management of Patients with Head Injuries. (2) 4 p.m., Dr. R. S. F. Schilling: Byssinosis in Textile Workers.

YORKSHIRE THORACIC SOCIETY.—At Instructional Block, Leeds General Infirmary, 5.30 p.m., Dr. J. G. Scadding: Some Observations on Chronic Interstitial Fibrosis of the Lungs.

Saturday, November 14

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Lecture Room B, Addenbrooke's Hospital, Cambridge, Symposium on Neurology. Morning: 10.30 a.m., Mr. W. S. Lewin: Purulent Infections of the Nervous System; 11.30 a.m., Dr. J. A. Campbell: Non-purulent Infections of the Nervous System; 12.15 p.m. Dr. H. W. Holland: Some Aspects of Neuroradiological Diagnosis. Afternoon: 2.30 p.m., Dr. M. F. T. Yealland: Lecture-demonstration of Some Neurological Cases.

Sunday, November 15

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS' NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Mr. W. F. Nicholson and Mr. A. G. Rendell: Cardiac Surgery.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Helsby.—On October 10, 1959, at his home, 1, Parke Road, Barnes, London, S.W., William George Helsby, M.R.C.S., L.R.C.P., aged 77.

MacLachlainn.—On October 9, 1959, at Royal Infirmary, Edinburgh, Alastair Mackintosh MacLachlainn, M.B., Ch.B., of Bad-daraich, Tobermory, Isle of Mull, Argyll.

Vickers.—On October 9, 1959, at 120, Street Lane, Leeds, Yorks, Benjamin Randall Vickers, M.B., B.S., aged 74.

Watt.—On October 10, 1959, in hospital, Thomas David Watt, M.B., Ch.B., of Buckley House, Walkden, near Manchester.

Wilson.—On October 3, 1959, in Italy, Edward Allan Wilson, M.D., of "Dalemoor," Bark Lane, Addingham, near Ilkley, Yorks, aged 79.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Emergency Transfusion

Q.—*Should any, and if so what, form of replacement transfusion be given before evacuation to hospital in cases of severe haemorrhage when blood is not available and it will take three to four hours before the patient arrives in hospital?*

A.—No patient with a serious haemorrhage from any cause should be allowed to run the risk of dying from acute oligaemia if plasma or a plasma-substitute, like dextran-saline, is available. These can be stored almost indefinitely without deterioration. Plasma or dextran should be transfused immediately, and kept going even while the patient is being transported to a hospital where blood transfusion and adequate surgical services are available. This is not necessarily the nearest hospital. A total of 2 to 12 pints (1.1–6.8 l.), or even more, may be necessary, depending on the circumstances. The patient may die from acute haemorrhagic anaemia if bleeding is heavy and prolonged (the lost red cells have not been replaced), but this risk is unavoidable in the circumstances.

The question of transporting blood rapidly to such emergencies must also be considered. This is basically a problem of organization; but in a country like Britain, where there is a highly organized and otherwise efficient system of regional blood transfusion services, it should be possible for certain regional centres to have helicopter facilities available at a moment's notice. In this way a supply of group O blood plus giving-sets can be flown to the patient, accompanied, if necessary, by a member of the staff of the transfusion service and a surgeon. The "flying squad" should truly fly in these circumstances.

Ultrasonics in Physiotherapy

Q.—*Are there any indications for ultrasonic therapy in physical medicine, and is it used in this country?*

A.—The effect of the application of ultrasonic waves is to produce a heating pattern. It is therefore a form of thermotherapy. It is claimed to be beneficial in the treatment of scar tissue, certain athletic injuries, and certain chronic inflammatory conditions. It may be potentially dangerous, especially to growing bones, nervous tissue, and the endocrine glands.

When first it was introduced there was some enthusiasm for this new form of treatment, but the enthusiasm has largely died down. The more familiar forms of thermotherapy, such as short-wave diathermy, should be more easily applied, be just as effective, and be safer. Many large physical medicine departments have not found it necessary to install ultrasonic emitters, and the Chartered Society of Physiotherapy has not included ultrasound therapy in its syllabus.

Secondary Malignant Melanoma of Lung

Q.—*A man of 45 who had a malignant melanoma excised from the chest wall two years ago, with block dissection of glands, now has at least two metastases in the lung. Is there any effective treatment for the metastases?*

A.—Malignant melanoma is a tumour with a high metastasizing potential. The treatment of metastases, other than in the regional lymph nodes, presents a most difficult problem. The majority of malignant melanomas are radio-resistant, and at the present time there is no effective chemotherapy. Endocrine surgery and hormone administration have nothing of value to offer. If the two metastases are in the same lung, or, better still, in the same lobe, and especially if they are situated in the periphery, cardiac catheterization into the pulmonary artery and perfusion with a solution of nitrogen mustard might prove of some benefit. The dose is 0.01 mg. per kilo body weight, and up to 10 mg. or more is given. Nitrogen mustard has a half-life of eight hours in normal saline, and allowance must be made for this factor when the perfusion lasts for eight hours; in this case the remainder of the solution will be one-half strength.

Susceptibility to Suggestion

Q.—*Why should a patient react favourably to suggestion under medical hypnosis when he is unable to react to the same suggestion simply by reassurance and relaxation?*

A.—Hypnotism is commonly regarded as bordering on the magical, and it is often assumed that the hypnotist has a special "gift." These ideas, although incorrect, can make hypnotism impressive as a form of treatment, and the susceptibility of a patient to suggestion is thereby increased. Consequently suggestions are readily received by certain patients and acted upon as though they sprang from the patient's mind. Unfortunately an attitude of dependence on the hypnotist can develop very quickly, and this also intensifies the suggestibility of the subject.

Reassurance and relaxation, while valuable, are less impressive. To be successful the reason behind them, given or implied, must be accepted by the patient. If the patient is not quite convinced, the reassurance with accompanying relaxation may evoke criticism rather than acceptance. The content of the suggestion, whether given with or without hypnosis, may be entirely reasonable, but no reasons are stated and so no opposition is aroused. Hence with selected patients the response is more favourable in the removal of symptoms. With some disabilities (e.g., psychical impotence) the removal of the symptom provides a strong and often lasting suggestion of success.

Reiter's Disease

Q.—*Is a wife liable to contract Reiter's disease from her husband? Is sterility a sequel of the syndrome?*

A.—Inasmuch as the causative agent of Reiter's disease has not yet been discovered, the answer to the first question can be based only on indirect evidence. As it is seen in this country, Reiter's disease may be considered as a clinical syndrome resulting from the development of complications of non-specific urogenital infection. These complications are arthritis, conjunctivitis or anterior uveitis, and lesions of the mucosae and skin.

Epidemiological studies provide little doubt that the urogenital infection is transmissible during sexual intercourse in the female, and may give rise to urethritis, cystitis, cervicitis, and salpingitis. The latter, if bilateral and severe, may result in sterility. However, for reasons which are not understood, the fully developed picture of Reiter's disease is very rarely seen in women.

It may therefore be said that the wife of a man suffering from Reiter's disease is likely to contract the urogenital infection. She is unlikely to develop the associated arthritis and surface lesions, but may become sterile if she develops pelvic infection.

Prednisolone Hemisuccinate

Q.—*Is prednisolone hemisuccinate, given intravenously, as effective as hydrocortisone hemisuccinate when given in one-fifth of the dose as recommended by the makers? Does it act as quickly as hydrocortisone?*

A.—Prednisolone is, weight for weight, about five times as potent as hydrocortisone as judged by such parameters as liver-glycogen deposition and antiphlogistic action. Hence the hemisuccinate salts of the two compounds have the same relationship. There is little data on the speed of action of prednisolone hemisuccinate, but it is unlikely on

theoretical grounds to differ materially from that of hydrocortisone hemisuccinate. Both compounds are equally effective in the emergency treatment of acute adrenal insufficiency, whether this is due to adrenal idiopathic atrophy, adrenal tuberculosis, or adrenal suppression secondary to administration of corticosteroids in the past. However, prednisolone has less sodium-retaining effect than hydrocortisone, and, although this is not of consequence in the immediate emergency treatment of such cases, as soon as oral administration is possible cortisone or hydrocortisone is to be preferred, since it will to some extent counteract the renal wastage of sodium that occurs in adrenal insufficiency.

Simultaneous Tetanus Toxoid and Antitoxin

Q.—*In cases of injury, is it reasonable to give tetanus toxoid at the same time as antitetanus serum, repeating the former a month later in order to give a permanent immunity, or does the synchronous dosage vitiate the effect of the toxoid?*

A.—The chief reason for not giving tetanus toxoid at the same time as tetanus antitoxin is that it is a waste of time. The toxoid is neutralized by the antitoxin and therefore cannot produce any antitoxin in the body. The injected antitoxin will, of course, confer passive immunity for a period of about two weeks, but the danger lies in the mistaken belief that the toxoid injected at the same time as the antitoxin is the beginning of a course of active immunization. In fact, it is not, and when the second dose of toxoid is given some six weeks later it acts as if it was the first dose and only at that time commences the production of antitoxin. The third dose of toxoid, given six months after the second dose, does not act as a third dose, as it is actually only the second dose of the course. This interval of six months is considered to be too long an interval between the first and second doses of a course of toxoid to ensure a satisfactory response to the second dose. If the injections cease at this point the course of toxoid will not have been a complete one and satisfactory active immunization will not have been induced.

The practice is now being widely adopted, as it already has been by the British Army, of delaying the start of the course of active immunization with tetanus toxoid until six to eight weeks after the injection of antitoxic serum.

Diet in Diverticulosis

Q.—*In preparing food for a patient with diverticulosis, when the avoidance of cellulose in pith and pip is important, is it advisable to use a food-shredder which will divide the food sufficiently finely to pass through a sieve?*

A.—The present position of dietary treatment for diverticulosis is far from satisfactory. There is a movement against the former rigid low-residue diet, which will encourage constipation. One merely wishes these patients to pass an easy, soft stool daily, and this is often best encouraged dietetically than by aperients. Patients with diverticulosis, and particularly those with diverticulitis, are probably more comfortable if they avoid root vegetables, which increase the amount of gas in the colon and hence cause distension and discomfort. Pips and skins may perhaps be excluded as a gesture to tradition, but there is certainly no case for using food-shredders or sieves.

Achlorhydria and Proctitis

Q.—*Can achlorhydria contribute to or even cause proctitis?*

A.—There is no evidence that achlorhydria contributes to the development of proctitis. There is certainly no special tendency for patients with Addisonian anaemia to develop proctitis. Proctitis is almost certainly a variant of ulcerative colitis, and 1 in 10 cases will develop into a full picture of colitis. Patients with proctitis are susceptible to fatigue and emotional trauma, and sometimes certain factors may precipitate bleeding.

Selenium Sulphide

Q.—*Is selenium sulphide, the active principle of a commonly used dandruff repressive shampoo, carcinogenic to humans?*

A.—There is no evidence to suggest that selenium sulphide is carcinogenic to humans. Selenium and its compounds have been used in industry for many years, and, although systemic poisoning and dermatitis may occur, carcinoma has not been recorded.

NOTES AND COMMENTS

Pseudomonas Pyocyanea Cystitis.—Dr. J. M. FRISCH (Burroughs Wellcome and Co.) writes: We would like to draw your attention to your column ("Any Questions?" August 29, p. 317) under the heading "*Pseudomonas pyocyanea* Cystitis." It is stated in the answer that "polymyxin is the most active of the antibiotics, but is regarded as too toxic for general use." This statement appears to be based on the original work on the toxicity of polymyxin A—the first polymyxin to be described. The polymyxin at present available is polymyxin B sulphate ("aerosporin"), which has now been in use for nearly 10 years and has been shown both experimentally and clinically to be safe when administered systemically in therapeutic dosage.[1–4] In view of the great value of polymyxin in infections which do not respond to other antibiotics and where it may be life-saving, we feel that its suitability for systemic administration should be more widely known. In cases of cystitis polymyxin may also be administered in 0.1 to 1% solution for irrigation of the bladder. As polymyxin is not absorbed from mucous membranes, this treatment is both highly effective and completely safe.

REFERENCES
1 Moyer, J. H., Mills, L. C., and Yow, E. M., *Arch. intern. Med.*, 1953, 92, 238.
2 Swift, P. N., and Bushby, S. R. M., *Lancet*, 1953, 1, 110.
3 Yow, E. M., and Moyer, J. H., *Clin. Res. Proc.*, 1953, 1, 47.
4 —— —— *Arch. intern. Med.*, 1953, 92, 248.

OUR EXPERT replies: Polymyxin A, the original antibiotic, was active against Gram-negative bacilli but was very toxic to the kidneys. Polymyxin B, the present preparation, is active against Gram-negative bacilli and is not toxic to the kidneys. It is only slightly painful when injected. Polymyxin D, although active against these bacilli, is not used, since it is toxic. Polymyxin E may be the best, since it is very active and non-toxic, but it is not commercially available. Polymyxin B would appear to be indicated in those cases of *pyocyanea* infection causing severe reaction, such as pyelonephritis or septicaemia, in which the organism is not sensitive to any other antibiotic or therapeutic agent. There is, however, considerable disagreement on whether it should be used just to get rid of an organism in the urine which is not causing a constitutional upset. Bladder washouts with a 1% solution are undoubtedly very effective and may be the answer to the latter condition.

Correction.—We regret that the name of Dr. G. N. ROLINSON, head of the Microbiological Research Unit at Beecham Laboratories, was wrongly given as Dr. Robinson in our report of his address on "The New Penicillins" at the Norwich Meeting (*Journal*, October 31, p. 880).

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